World Health Organization

CERVICAL CANCER SCREENING

VOLUME 18

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

IARC HANDBOOKS

CERVICAL CANCER SCREENING

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This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Strategies, which met in Lyon, 12–16 October 2020

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IARC HANDBOOKS OF CANCER PREVENTION

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The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly, as an independently funded organization within the framework of the World Health Organization. The headquarters of the Agency are in Lyon, France.

The Agency has as its mission to reduce the cancer burden worldwide through promoting international collaboration in research. The Agency addresses this mission through conducting cancer research for cancer prevention in three main areas: describing the occurrence of cancer; identifying the causes of cancer, and evaluating preventive interventions and their implementation. Each of these areas is a vital contribution to the spectrum of cancer prevention.

The publications of the Agency contribute to the dissemination of authoritative information on different aspects of cancer research. Information about IARC publications, and how to order them, is available at https://publications.iarc.fr/.

IARC Handbooks of Cancer Prevention

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of monographs of critical reviews and evaluations of individual chemicals.

The *IARC Handbooks of Cancer Prevention* complement the *IARC Monographs*' identifications of carcinogenic hazards. The objective of the programme is to coordinate and publish critical reviews of data on the cancer-preventive effects of primary or secondary interventions, and to evaluate these data in terms of cancer prevention with the help of international working groups of experts in prevention and related fields. The lists of evaluations are regularly updated and are available at https://handbooks.iarc.fr/.
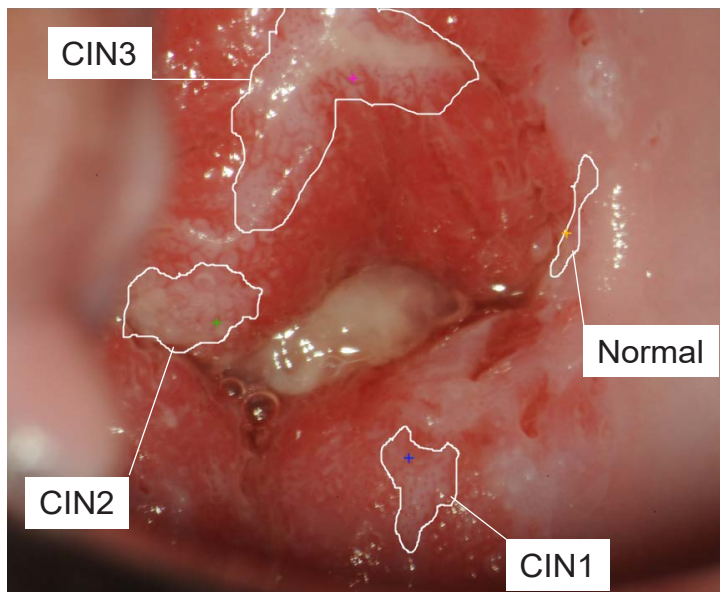
Cover image: Photograph of the cervix uteri of a 19-year-old woman, with identified cervical lesions. Normal, normal tissue. CIN, cervical intraepithelial neoplasia. The numbering defines the grade (1, 2, or 3) of the lesion. ©Nicolas Wentzensen

CONTENTS

NOTE TO THE READER

The *IARC Handbooks of Cancer Prevention* series was launched in 1995 to complement the *IARC Monographs*' evaluations of carcinogenic hazards. The *IARC Handbooks of Cancer Prevention* evaluate the published scientific evidence of cancer-preventive interventions.

Inclusion of an intervention in the *Handbooks* does not imply that it is cancer-preventive, only that the published data have been examined. Equally, the fact that an intervention has not yet been evaluated in a *Handbook* does not mean that it may not prevent cancer. Similarly, identification of organ sites with *sufficient evidence* or *limited evidence* that the intervention has a cancer-preventive activity in humans should not be viewed as precluding the possibility that an intervention may prevent cancer at other sites.

The evaluations of cancer-preventive interventions are made by international Working Groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of cancer-preventive interventions is encouraged to make this information available to the *IARC Handbooks* programme, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, or by email to ihb@iarc.fr, in order that these data may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Handbooks* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the *IARC Handbooks* programme at ihb@iarc.fr. Corrigenda are published online on the relevant webpage for the volume concerned (IARC Publications: https://publications.iarc.fr/).

LIST OF PARTICIPANTS

Members [1]

Silvina Arrossi

> Center for the Study of State and Society/National Council for Scientific and Technical Research (CEDES/CONICET)
> Buenos Aires
> Argentina

Karima Bendahhou

> Casablanca Cancer Registry
> Centre Mohammed VI pour le traitement des cancers
> Casablanca
> Morocco

Johannes Berkhof (Subgroup Chair, Preventive and Adverse Effects of HPV Tests)

> Department of Epidemiology and Data Science
> Amsterdam University Medical Centers
> Amsterdam
> The Netherlands

Julia Brotherton [2] (Subgroup Chair, Preventive and Adverse Effects of Visual and Cytological Methods)

> VCS Foundation Ltd
> Melbourne
> Australia

---

[1] Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only. Invited Specialists do not serve as Meeting Chair or Subgroup Chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations. Each participant was asked to declare potentially relevant research, employment, and financial interests that are current or that have occurred during the past 4 years. Minimal interests are not disclosed here and include stock valued at no more than US$ 1000 overall, grants that provide no more than 5% of the research budget of the expert's organization and that do not support the expert's research or position, and consulting or speaking on matters not before a court or government agency that does not exceed 2% of total professional time or compensation. All other non-publicly funded grants that support the expert's research or position and all consulting or speaking on behalf of an interested party on matters before a court or government agency are disclosed as potentially significant conflicts of interests.

[2] Julia Brotherton reports that her unit at VCS Population Health benefits from research funding and equipment from Roche, Seegene, Cepheid, and Becton Dickinson.

Karen Canfell

The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council NSW
Woolloomooloo
Australia

Z. Mike Chirenje

University of Zimbabwe College of Health Sciences - Clinical Trials Research Centre (UZCHS-CTRC)
Harare
Zimbabwe

Michael H. Chung

Division of Infectious Diseases
Department of Medicine
Emory University
Atlanta, GA
USA

Marta del Pino

Gynecologic Oncology Unit
Clinical Institute of Gynecology, Obstetrics and Neonatology (ICGON)
Hospital Clínic de Barcelona
Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
University of Barcelona
Barcelona
Spain

Silvia de Sanjosé

Reproductive Health Global Program
PATH
Seattle, WA
USA

Miriam Elfström [3]

Center for Cervical Cancer Prevention
Karolinska University Hospital
Department of Laboratory Medicine
Karolinska Institutet
Huddinge
Sweden

Eduardo Franco [4]

Division of Cancer Epidemiology
McGill University
Montreal, Quebec
Canada

Paolo Giorgi-Rossi (Subgroup Vice-Chair, Preventive and Adverse Effects of Visual and Cytological Methods)

Epidemiology Unit
Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia
Reggio Emilia
Italy

Chisato Hamashima

Teikyo University
and
National Cancer Center of Japan
Tokyo
Japan

Françoise F. Hamers

French National Public Health Agency
Saint-Maurice
France

C. Simon Herrington

Institute of Genetics and Molecular Medicine
(IGMM)
Division of Pathology
University of Edinburgh
Edinburgh
United Kingdom

Rachel Kupets (Subgroup Chair, Cervical Cancer and Screening Practices)

Division of Gynecologic Oncology
University of Toronto
Ontario Cervical Cancer Screening Program
Cancer Prevention, Cancer Care Ontario
Toronto, Ontario
Canada

Anne Mackie (Meeting Co-Chair)

Public Health England Screening
London
United Kingdom

Raúl Murillo

Centro Javeriano de Oncología
Hospital Universitario San Ignacio
Facultad de Medicina
Pontificia Universidad Javeriana
Bogotá
Colombia

Suleeporn Sangrajrang

National Cancer Institute
Bangkok
Thailand

Rengaswamy Sankaranarayanan

RTI International India
New Delhi
India

Mona Saraiya

Centers for Disease Control and Prevention
Atlanta, GA
USA

Mark Schiffman [5]

Clinical Epidemiology Unit
Clinical Genetics Branch
Division of Cancer Epidemiology and
Genetics
National Cancer Institute
Rockville, MD
USA

Robert Smith (Subgroup Chair, Differential-Risk Populations and Screen-and-Treat)

American Cancer Society
Atlanta, GA
USA

---

[5] Mark Schiffman reports that his unit at the National Cancer Institute benefited from equipment and supplies from Qiagen and MobileODT.

Nicolas Wentzensen (Meeting Co-Chair)

Clinical Epidemiology Unit
Clinical Genetics Branch
Division of Cancer Epidemiology and
    Genetics
National Cancer Institute
Rockville, MD
USA

Fanghui Zhao

Department of Cancer Epidemiology
National Cancer Center and Cancer Hospital
Chinese Academy of Medical Sciences
Beijing
China

Invited Specialists

Marc Arbyn [6]

Sciensano
Brussels
Belgium

Walter Prendiville [7]

Senior Visiting Scientist
International Agency for Research on Cancer
Lyon
France

Representative

Carolina Wiesner

Colombian National Cancer Institute
Bogotá
Colombia

Observer [8]

Jae-Weon Kim

Department of Obstetrics and Gynecology
Seoul National University College of
    Medicine
Seoul
Republic of Korea

IARC/WHO Secretariat

Maribel Almonte, Head, Prevention and
    Implementation Group
Armando Baena, Prevention and
    Implementation Group
Partha Basu, Head, Screening Group
Iacopo Baussano, Infections and Cancer
    Epidemiology Group

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[6] Marc Arbyn reports that his unit at Sciensano benefits from non-monetary support from manufacturers of human papillomavirus (HPV) assays and devices.

[7] Walter Prendiville reports holding stocks in NSV, receiving consultancy fees from Koru Auckland, and receiving royalties from Utah Medical Products, Inc. for patent #5951550.

[8] Each Observer agreed to respect the Guidelines for Observers at *IARC Handbooks* meetings. Observers did not serve as Meeting Chair or Subgroup Chair, draft or revise any part of the *Handbook*, or participate in the evaluations. They also agreed not to contact participants before or after the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group Members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.

Véronique Bouvard, IARC Handbooks Group *(Co-Responsible Officer, Co-Rapporteur)*

Nathalie Broutet, WHO headquarters

Citadel Cabasag, Section of Cancer Surveillance

Gary Clifford, Head, Infections and Cancer Epidemiology Group

Ian Cree, Head, Section of Evidence Synthesis and Classification

Hugo De Vuyst, Prevention and Implementation Group

Carolina Espina Garcia, Section of Environment and Radiation

Elena Fidarova, WHO headquarters

Mathilde Forestier, Visiting Scientist, Prevention and Implementation Group

John Grove, WHO headquarters

Isabelle Heard, Visiting Scientist, Prevention and Implementation Group

Blanca Iciar Indave, WHO Classification of Tumours Group *(Co-Rapporteur)*

Béatrice Lauby-Secretan, Head, IARC Handbooks Group *(Co-Responsible Officer, Co-Rapporteur)*

Isabel Mosquera-Metcalfe, Screening Group *(Co-Rapporteur)*

Karen Müller, Communications Group *(Editor)*

Tatiana Ramirez, Prevention and Implementation Group

Mariluz Rol, Prevention and Implementation Group

Guglielmo Ronco, Visiting Scientist, Infections and Cancer Epidemiology Group

Nancy Santesso, WHO headquarters

Catherine Sauvaget, Screening Group

Farida Selmouni, Screening Group

Vitaly Smelov, Prevention and Implementation Group [unable to attend]

Salvatore Vaccarella, Section of Cancer Surveillance [unable to attend]

Patricia Villain, Screening Group

Administrative Assistance

Marieke Dusenberg

Michel Javin

Jennifer Nicholson

Production Team

Fiona Gould

Niree Kraushaar

Solène Quennehen

Scientific Assistance

Armando Baena, IARC

Mónica Ballesteros Silva

Dominika Bhatia

Helen Kelly

Tatiana Ramirez, IARC

Remila Rezhake

Joan Valls Marsal, IARC

Post-Meeting Assistance

Harriet Stewart-Jones *(Scientific Editor)*

PREAMBLE – SECONDARY PREVENTION

The Preamble to the *IARC Handbooks of Cancer Prevention* describes the objectives and scope of the programme, general principles and procedures, and scientific review and evaluations. The *IARC Handbooks* embody the principles of scientific rigour, impartial evaluation, transparency, and consistency. The Preamble should be consulted when reading an *IARC Handbook* or a summary of an *IARC Handbook*'s evaluations. Separate Instructions for Authors describe the operational procedures for the preparation and publication of a volume of the *IARC Handbooks*.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Prevention of cancer is the mission of the International Agency for Research on Cancer (IARC). Cancer prevention is needed even more today than when IARC was established, in 1965, because the global burden of cancer is high and continues to increase, as a result of population growth and ageing and increases in cancer-causing exposures and behaviours, especially in low- and middle-income countries (Stewart & Kleihues, 2003; Boyle & Levin, 2008; Stewart & Wild, 2014).

Broadly defined, prevention is "actions aimed at eradicating, eliminating, or minimizing the impact of disease and disability, or if none of these is feasible, retarding the progress of disease and disability" (Porta, 2014). Cancer prevention encompasses primary, secondary, and tertiary prevention. Primary prevention consists of actions that can be taken to lower the risk of developing cancer. Secondary prevention entails methods that can find and ameliorate precancerous conditions or find cancers in the early stages, when they can be treated more successfully. Tertiary prevention is the application of measures aimed at reducing the impact of long-term disease and disability caused by cancer or its treatment.

The *IARC Handbooks of Cancer Prevention* provide critical reviews and evaluations of the scientific evidence on the preventive effects of primary or secondary cancer prevention measures. The evaluations of the *IARC Handbooks* are used by national and international health agencies to develop evidence-based interventions or recommendations for reducing cancer risk.

The *IARC Handbooks of Cancer Prevention* series was launched in 1995 by Dr Paul Kleihues, then Director of IARC, in recognition of the need for a series of publications that would critically review and evaluate the evidence on a wide range of cancer-preventive interventions. The first volume of the *IARC Handbooks* (IARC,

1997) reviewed the evidence on cancer-preventive effects of non-steroidal anti-inflammatory drugs, specifically aspirin, sulindac, piroxicam, and indomethacin. *Handbooks* Volume 6 (IARC, 2002a) was the first that evaluated behavioural interventions (weight control and physical activity), and *Handbooks* Volume 7 (IARC, 2002b) was the first that evaluated cancer screening (breast cancer screening). *Handbooks* Volumes 11–14 (IARC, 2007, 2008, 2009, 2011) focused on tobacco control. After a 3-year hiatus, the *IARC Handbooks* series was relaunched in 2014 with the preparation of *Handbooks* Volume 15 (IARC, 2016a), which re-evaluated breast cancer screening.

IARC's process for developing *Handbooks* engages international, expert scientific Working Groups in a transparent synthesis of different streams of evidence, which is then translated into an overall evaluation according to criteria that IARC has developed and refined (see Part A, Section 6). Scientific advances are periodically incorporated into the evaluation methodology, which must enable the evaluation of new generations of existing methods as well as new screening methodologies.

This Preamble, first prepared as the *Handbooks* Working Procedures in 1995 and later adapted to the topics of cancer screening and tobacco control, is primarily a statement of the general principles and procedures used in developing a *Handbook*, to promote transparency and consistency across *Handbooks* evaluations. In addition, IARC provides Instructions for Authors to specify more detailed operating procedures.

2. Objectives, scope, and definitions

2.1 Objectives and scope

The scope of the *IARC Handbooks of Cancer Prevention* series is to contribute to reducing the incidence of or mortality from cancer worldwide. To this end, the *IARC Handbooks* programme prepares and publishes, in the form of volumes of *Handbooks*, critical scientific reviews and evaluations of the available evidence on the efficacy, effectiveness, and harms of a wide range of cancer-preventive interventions. The primary target audiences for the *Handbooks* are national and international agencies with responsibility for, or advocating for, public health. The *IARC Handbooks* are an important part of the body of information on which public health decisions for cancer prevention may be based. However, public health options to prevent cancer vary from one setting to another and from country to country, and relate to many factors, including socioeconomic conditions and national priorities. Therefore, no recommendations are given in the *Handbooks* with regard to regulations or legislation, which are the responsibility of individual governments or other international authorities. However, the *IARC Handbooks* may aid national and international authorities in devising programmes of health promotion and cancer prevention, estimating the balance of benefits and harms, and considering cost–effectiveness evaluations.

The *IARC Handbooks* programme also does not make formal research recommendations. However, because *Handbooks* synthesize and integrate streams of evidence on cancer prevention, critical gaps in knowledge that merit research may be identified.

2.2 Definition of interventions for secondary prevention

The current *IARC Handbook* addresses a specific intervention or class of interventions for **secondary prevention**. The principal instruments of secondary prevention of cancer are interventions for early detection of precancerous lesions (i.e. precancer) or invasive cancer, which are currently mostly cancer screening interventions. However, there is growing evidence that action campaigns to increase awareness of cancer among the general public can increase the number of people who present to health-care providers, leading to earlier diagnosis of cancer and, generally, to better cancer outcomes. Such interventions for early diagnosis are also within the scope of the *Handbooks* programme.

Screening is the systematic application of a test that "can be applied rapidly in a presumably asymptomatic population, aiming at the presumptive identification of unrecognized disease or defect" (Porta, 2014). Screening tests sort out apparently-well people who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic, because people with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment (Porta, 2014). Screening may enable diagnosis of cancer sufficiently early that cure and resulting prevention of cancer death or a reduction in risk of cancer are realistic possibilities. Screening for some cancers, such as cervical cancer or colorectal cancer, may also detect precancer, effective treatment of which can prevent occurrence of invasive cancer. Screening can also cause harm, and evidence for harm must also be considered when evaluating the capacity of screening to reduce the incidence of cancer or death from cancer.

Screening interventions can be applied across a continuum of:

(i) the general population (often circumscribed by age and sex);

(ii) subgroups with particular predisposing host characteristics, such as genetic susceptibility, precursor lesions, or particular diseases other than cancer, or with high exposure to environmental, occupational, or behavioural risk factors; and

(iii) people with a history of cancer who are at high risk of a further primary cancer.

Early diagnosis interventions aim at detecting cancer in symptomatic patients as early as possible. Delays in accessing cancer care are common with late-stage presentation, particularly in lower-resource settings and in vulnerable populations. The consequences of delayed or inaccessible cancer care are lower likelihood of survival, greater morbidity of treatment, and higher costs of care, resulting in avoidable deaths and disability from cancer. Early diagnosis improves cancer outcomes by providing care at the earliest possible stage and is therefore an important public health strategy in all settings (https://www.who.int/cancer/prevention/diagnosis-screening/en/). One of the most commonly used strategies is to raise awareness among the public and/or health professionals of early signs and symptoms of cancer in order to facilitate diagnosis before the disease becomes advanced. Other possible interventions to promote early diagnosis may involve regulation of health care and organization of health services (WHO, 2017).

2.3 Definitions of efficacy, effectiveness, and harms

Efficacy and effectiveness are two fundamental concepts underlying the evaluation of preventive interventions (Cochrane, 1972). Efficacy was defined by Porta (2008) as "the extent to which a specific intervention, procedure, regimen or service produces a beneficial result under ideal conditions … Ideally, the determination of efficacy is based on the results

of a randomized controlled trial". Effectiveness was defined by Porta (2008) as "a measure of the extent to which a specific intervention, procedure, regimen or service, when deployed in the field in routine circumstances, does what it is intended to do for a specific population".

The distinction between efficacy and effectiveness of an intervention at the population level is an important one to make when evaluating preventive interventions. Efficacy is a necessary, but not sufficient, basis for formulating recommendations for an intervention. Whereas efficacy of an intervention can be inferred if effectiveness is established, efficacy does not guarantee effectiveness because of the number of implementation steps, each with uncertainty, required to deliver an efficacious prevention intervention as an effective programme in a target population. Ideally, efficacy is established before a preventive intervention is implemented in a whole community or population, so as to determine whether a case for population-wide implementation can be made on the basis of the balance of the benefits and harms and the financial costs of the intervention. However, it has not been unusual for preventive interventions to be implemented in the absence of evidence of efficacy. Should that occur, evaluation of effectiveness may be the only way to determine whether the case for the intervention is strong enough to justify its continuation or implementation elsewhere.

In addition to being shown to be efficacious or effective, screening interventions must satisfy other requirements if they are to be considered for implementation in practice, including an acceptable balance of benefits and harms. In the present context, harm is defined as any impairment or increase in risk of impairment as a result of exposure to or participation in a preventive intervention. Harms include physical, psychological, social, and economic consequences of a preventive intervention. Adverse events in health care are a subset of harms. Evaluation of these potential harms is an important component of the summary of the evidence.

For screening and for early diagnosis, other issues to be considered include acceptability to the target population, impact on health equity, cost, cost–effectiveness, availability of the personnel and facilities required to deliver the screening intervention, and access to the health services needed to diagnose and treat the disease detected. Depending on the specific intervention, some of these issues may be of sufficiently high interest to programme managers that they, too, are reviewed in the *IARC Handbook*.

Although the distinction between evidence of efficacy and effectiveness is an important one to make when seeking to act on cancer prevention, the *Handbooks* evaluations are based on evidence from **all** relevant research into efficacy and effectiveness.

3. Identification and selection of interventions and outcomes for review

3.1 Development of an analytical framework

As one of the first steps in the review and evaluation of a selected cancer screening intervention, the IARC Secretariat, with the support of the Working Group, drafts an analytical framework. Such a framework depicts the relationships among the study population, intervention, comparator, and intermediate outcomes or changes in health status as relevant. The analytical framework includes both benefits and harms, and key contextual issues related to participation and implementation of the intervention and its impact on population health. The framework defines the intervention in its broadest context and specifies the aspects for which the *Handbook* will review and evaluate the evidence.

In this framework, it is most commonly the case that a single cancer type, usually only topographically defined, is the primary target, and the reduction of the incidence of and/or mortality from that cancer type is the primary outcome. However, it is sometimes the case that intermediate outcomes (i.e. outcomes that are not invasive cancer or death from cancer) are important targets. For example, detection and ablation of precancerous polyps is the mechanism whereby some screening methods for colon cancer and rectal cancer reduce the incidence of colorectal cancer. Moreover, it is plausible that a new test with high sensitivity and specificity for a precancerous lesion, such as high-grade cervical intraepithelial neoplasia, could be judged on the grounds of these characteristics to be efficacious in preventing invasive cervical cancer and death from cervical cancer, provided that there is also strong evidence that ablation of the precancerous lesion prevents invasive cervical cancer. These possibilities are taken into consideration when defining the framework of a *Handbook*.

3.2 Selection of the interventions

For each new volume of the *Handbooks*, IARC selects one or more interventions for review by considering the availability of pertinent research studies, the need to evaluate an important development in cancer prevention, or the need to re-evaluate a previously evaluated intervention. IARC will also consider current public health priorities in specific geographical regions, for example the concerns of countries or regions with a high risk of specific cancer types (see Part A, Section 6, Step 1).

Interventions not previously evaluated in the *IARC Handbooks* series are selected for evaluation, where the body of evidence is large enough to warrant evaluation, on the basis of one or both of the following criteria:

- The intervention is of putative preventive value, but its effects or balance of benefits and harms have not been established formally;
- The available evidence suggests that the intervention has the potential to significantly reduce the incidence of or mortality from cancer, or to have a significant impact on an intermediate outcome (e.g. precancerous lesions; see below) known or highly suspected to be linked to cancer (see Part A, Section 6, Step 2).

In addition, an intervention previously evaluated in a *Handbook* may be re-evaluated if important new data become available about its effects, or if its technology or implementation has changed enough for there to be substantial changes in its effects. Occasionally, a re-evaluation may be limited to specific aspects of the screening intervention to which the new evidence predominantly relates (e.g. tomosynthesis for breast cancer screening). For re-evaluations, the full body of evidence relevant to the intervention of interest is considered, either by de novo review of all evidence or by accepting as accurate the evidence review of the previously published *Handbook* and undertaking a de novo review of evidence published since the previous review. Both approaches lead to an evaluation based on all relevant evidence (see Part A, Section 6, Steps 4 and 5). The choice of the approach is subject to the judgement of the Working Group.

4. The Working Group and other meeting participants

Five categories of participants can be present at *IARC Handbooks* meetings (Table 1):

(i) *Working Group* members have ultimate responsibility for determining the final list of studies that contribute evidence to the evaluation, performing the scientific review of the evidence, and making the final, formal

Table 1 Roles of participants at *IARC Handbooks* meetings

Category of participant	Role			
	Prepare text, tables, and analyses	Participate in discussions	Participate in evaluations	Eligible to serve as Meeting Chair or Subgroup Chair
Working Group members	✓	✓	✓	✓
Invited Specialists	✓[a]	✓		
Representatives of health agencies		✓[b]		
Observers		✓[b]		
IARC Secretariat	✓[c]	✓	✓[d]	

[a] Only for sections not directly relevant to the evaluation
[b] Only at times designated by the Meeting Chair and/or Subgroup Chair
[c] Only when needed or requested by the Meeting Chair and/or Subgroup Chair
[d] Only for supporting Working Group members and for clarifying or interpreting the Preamble

evaluation of the strength of evidence for the capacity of the screening interventions to reduce cancer incidence or cancer mortality. The Working Group is multidisciplinary and is organized into Subgroups of experts in the fields that the *Handbook* covers.

IARC selects the Working Group members on the basis of relevant expertise and an assessment of declared interests (see Part A, Section 5). For screening, the fields of expertise are: (i) the cancer targeted and its global epidemiology; (ii) worldwide use of preventive interventions for the cancer targeted; and (iii) specific knowledge and experience of screening, in general or as practised for the targeted cancer. Consideration is also given to diversity in scientific approaches, in stated positions on the strength of the evidence supporting the intervention, and in demographic characteristics. Working Group members generally have published research related to the interventions being reviewed or to the cancer types or intermediate outcomes that the interventions being reviewed are thought to prevent; IARC uses literature searches to identify most experts. IARC also encourages public nominations through its Call for Experts. IARC's reliance on Working Group members with expertise on the subject

matter or relevant methodologies is supported by decades of experience documenting that there is value in specialized expertise and that the overwhelming majority of Working Group members are committed to the objective evaluation of scientific evidence and not to the narrow advancement of their own research results or a predetermined outcome ([Wild & Cogliano, 2011](#)). Working Group members are expected to serve the public health mission of IARC and to refrain from using inside information from the meeting or meeting drafts for financial gain until the full volume of the *Handbooks* is published (see also Part A, Section 7).

IARC selects, from among the Working Group members, individuals to serve as Meeting Chair and Subgroup Chairs. Subgroup Chairs have preferably served in previous *Handbooks* meetings as Working Group members or in similar review processes. At the opening of the meeting, the Working Group is asked to endorse the Meeting Chair selected by IARC or to propose an alternative. The Meeting Chair and Subgroup Chairs take a leading role at all stages of the review process (see Part A, Section 7) to promote open scientific discussions that involve all Working Group members in accordance

with committee procedures and to ensure adherence to the processes described in this Preamble.

(ii) *Invited Specialists* are experts with critical knowledge and experience on the interventions being reviewed, the cancer types that the interventions being reviewed are thought to prevent, or relevant methodologies, but who have a declared conflict of interests that warrants exclusion from developing or influencing the evaluations. The Invited Specialists do not draft any section of the *Handbook* that pertains to the description or interpretation of the data on which the evaluation is based, or participate in the evaluations. Invited Specialists are invited in limited numbers, when necessary, to assist the Working Group by contributing their unique knowledge and experience to the discussions.

(iii) *Representatives of national and international health agencies* may attend because their agencies are interested in the subject of the *Handbook*. The Representatives of national and international health agencies do not draft any section of the *Handbook* or participate in the evaluations. Representatives can participate in discussions at times designated by the Meeting Chair or a Subgroup Chair. Relevant World Health Organization (WHO) staff members attend as members of the *IARC Secretariat* (see below).

(iv) *Observers* with relevant scientific credentials are admitted in limited numbers. Attention is given to the balance of Observers from entities with differing perspectives on the interventions under review. Observers are invited only to observe the meeting, do not draft any section of the *Handbook* or participate in the evaluations, must agree to respect the Guidelines for Observers at *IARC Handbooks* meetings (IARC, 2018), and must not attempt to influence the outcomes of the meeting. Observers may speak at Working Group or Subgroup sessions at the discretion of the Chair.

(v) The *IARC Secretariat* consists of scientists who are designated by IARC or WHO and who have relevant expertise. The IARC Secretariat coordinates and facilitates all aspects of the review and evaluation process and ensures adherence to the processes described in this Preamble throughout the development of the scientific reviews and evaluations (see Part A, Sections 5 and 6). The IARC Secretariat announces and organizes the meeting, identifies and invites the Working Group members, and assesses the declared interests of all meeting participants in accordance with WHO requirements (see Part A, Section 5). The IARC Secretariat supports the activities of the Working Group (see Part A, Section 7) by performing systematic literature searches, performing title and abstract screening, organizing conference calls to coordinate the development of drafts and to discuss cross-cutting issues, and reviewing drafts before and during the meeting. Members of the IARC Secretariat serve as meeting rapporteurs, assist the Meeting Chair and Subgroup Chairs in facilitating all discussions, and may draft text or tables or assist a Subgroup in the conduct of additional analyses when designated by the Meeting Chair or a Subgroup Chair. After the meeting, the IARC Secretariat reviews the drafts for factual accuracy of research results cited. The participation of the IARC Secretariat in the evaluations is restricted to clarifying or interpreting the Preamble.

All meeting participants are listed, with their principal affiliations, in the front matter of the published volume of the *Handbooks*. Pertinent interests, if any, are listed in a footnote to the participant's name. Working Group members and Invited Specialists serve as individual scientists

and not as representatives of any organization, government, or industry (Cogliano et al., 2004).

The roles of the participants are summarized in Table 1.

5. Development of a volume of the *IARC Handbooks*

Each volume of the *Handbooks* is developed by an ad hoc, specifically convened Working Group of international experts. Approximately 1 year before the meeting of a Working Group, a preliminary list of interventions to be reviewed (see Part A, Section 3), together with a Call for Data and a Call for Experts, is announced on the *Handbooks* programme website (https://handbooks.iarc.fr/).

The IARC Secretariat selects potential Working Group members based on the criteria described in Part A, Section 4. Before a meeting invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests form to report financial interests, employment and consulting (including remuneration for serving as an expert witness), individual and institutional research support, and non-financial interests such as public statements and positions related to the subject of the meeting. IARC assesses the declared interests to determine whether there is a conflict that warrants any limitation on participation (see Table 1).

Approximately 2 months before a meeting, IARC publishes on the *Handbooks* programme website the names and principal affiliations of all participants and discloses any pertinent and significant conflicts of interests, for transparency and to provide an opportunity for undeclared conflicts of interests to be brought to IARC's attention. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

The Working Group meets at IARC to discuss and finalize the scientific review and to develop summaries and evaluations. At the opening of the meeting, all meeting participants update their Declarations of Interests forms, which are then reviewed for conflicts of interest by IARC. Declared interests related to the subject of the meeting are disclosed to the meeting participants during the meeting and in the published volume of the *Handbooks* (Cogliano et al., 2004).

The objectives of the meeting are twofold: peer review of the drafts and consensus on the evaluations. During the first part of the meeting, Working Group members work in Subgroups to review the pre-meeting drafts, develop a joint Subgroup draft, and draft Subgroup summaries. During the last part of the meeting, the Working Group meets in plenary sessions to review the Subgroup drafts and summaries and to develop the consensus evaluations. As a result, the entire volume is the joint product of the Working Group and there are no individually authored sections. After the meeting, the master copy is verified by the IARC Secretariat (see Part A, Section 4(v)), edited, and prepared for publication. The aim is to publish the volume of the *Handbooks* within approximately 12 months of the Working Group meeting. The IARC Secretariat prepares a summary of the outcome for publication in a scientific journal or on the *Handbooks* programme website soon after the meeting.

The time frame and milestones for public engagement during the development of a volume of the *IARC Handbooks* are summarized in Table 2.

Table 2 Public engagement during the development of a volume of the *IARC Handbooks*

Approximate time frame	Milestones
~1 year before a *Handbooks* meeting	IARC posts on the *Handbooks* programme website: Preliminary List of Interventions to be reviewed Call for Data and Call for Experts open Requests for Observer Status open WHO Declarations of Interests form
~8 months before a *Handbooks* meeting	Call for Experts closes
~4 months before a *Handbooks* meeting	Requests for Observer Status close
~2 months before a *Handbooks* meeting	IARC publishes the names, principal affiliations, and declared conflicts of interest of all meeting participants, and a statement discouraging contact of Working Group members by outside parties
~1 month before a *Handbooks* meeting	Call for Data closes
***Handbooks* meeting**	
~2–4 months after a *Handbooks* meeting	IARC publishes a summary of evaluations and key supporting evidence as a scientific article in a high-impact journal or on the *Handbooks* programme website
~9–12 months after a *Handbooks* meeting	IARC Secretariat publishes the verified and edited master copy of the plenary drafts as a *Handbooks* volume

6. Overview of the scientific review and evaluation process

Principles of systematic review are applied to the identification, screening, synthesis, and evaluation of the evidence (as described in Part B, Sections 2–7 and detailed in the Instructions for Authors). For each volume of the *Handbooks*, the information on the conduct of the literature searches, including search terms and the inclusion and exclusion criteria that were used for each relevant stream of evidence, is recorded.

The Working Group considers all relevant studies, including experimental and observational studies of the efficacy and/or effectiveness of the intervention and related harms (including systematic reviews and meta-analyses), pertinent information on global practices of the screening methods, and background information on the global epidemiology and burden of the targeted cancer type.

In general, only studies that have been published or accepted for publication in the openly available scientific literature are reviewed.

Materials that are publicly available and whose content is final may be reviewed if there is sufficient information to enable peer evaluation of the quality of the methods and results of the studies (see Step 1, below). Such material may include reports from government agencies, dissertations for higher degrees, and other apparently reputable scientific sources. Systematic Internet searches for potentially relevant "grey literature" are not usually done. The reliance on published and publicly available studies promotes transparency and protects against citation of information that, although purportedly final, may change before it is published.

The steps of the review process are as follows:

Step 1. Identification of the review question: After the intervention (or interventions) and outcome (or outcomes) to be reviewed have been specified, the IARC Secretariat, in consultation with the Working Group, drafts the review question (or questions) in PICO form (population, intervention/exposure, comparator, and outcome) as required to determine the inclusion and exclusion criteria for the studies. An

analytical framework is developed to assist in identifying and formulating the review questions, with the aim of making as large a contribution as possible to the global prevention of cancer.

Step 2. Comprehensive and transparent identification of the relevant information: The IARC Secretariat specifies search terms for the key PICO components of each question and identifies relevant studies through initial comprehensive literature searches in authoritative biomedical databases (e.g. PubMed). The literature searches are designed in consultation with a librarian and other technical experts. The scope and specifications of the searches may be modified, and the searches rerun, depending on the amount, relevance, and perceived completeness of the articles they identify. The IARC Secretariat may also identify relevant studies from reference lists of past *Handbooks*, retrieved articles, or authoritative reviews, and through the Call for Data (see Table 2). The Working Group provides input and advice to the IARC Secretariat to refine the search strategies, and identifies additional articles through other searches and personal expert knowledge.

For certain types of interventions (e.g. administration of regulated imaging agents), IARC also gives relevant regulatory authorities, and parties regulated by such authorities, an opportunity to make pertinent unpublished studies publicly available by the date specified in the Call for Data. Consideration of such studies by the Working Group is dependent on the public availability of sufficient information to enable an independent peer evaluation of: (i) completeness of reporting of pertinent data; (ii) study quality; and (iii) study results.

Step 3. Screening, selection, and organization of the studies: The IARC Secretariat screens the retrieved articles by reviewing the title and abstract against the inclusion and exclusion criteria agreed upon by the Working Group and technical experts in the review process. Potentially relevant studies are then made available to Working Group members for full-text screening and inclusion in or exclusion from the evidence base using agreed criteria specific to this task.

Step 4. Extraction of information from included studies, including characteristics relevant to study quality: Working Group members, working individually as members of defined Subgroups before the *Handbooks* meeting, review and succinctly describe pertinent characteristics and results of included studies as detailed in Part B, Sections 2–5. Study design and results are tabulated systematically in a standard format. This step may be iterative with Step 5.

Step 5. Assessment of study quality: Also before the *Handbooks* meeting, Working Group members evaluate the quality and informativeness of each study they included based on the considerations (e.g. design, conduct, analysis, and reporting of results) described in Part B, Sections 2–5. Evaluation of study quality can be done either narratively or by use of a risk of bias assessment tool when a relevant one is available and can add value to the process. Interpretations of the results, and the strengths and limitations of each study, are clearly outlined in square brackets as part of the description of that study (see Part B).

Step 6. Peer review: Several months before the meeting, the pre-meeting drafts produced from Steps 4 and 5 are peer-reviewed by other members of the Working Group (usually within the same Subgroup). The IARC Secretariat also reviews the drafts for completeness, consistency between drafts, and adherence to the *Handbooks* Instructions for Authors. The peer-review comments are sent to the Working Group members, who produce a revised pre-meeting draft. The revised drafts are reviewed and revised in Subgroup sessions during the *Handbooks* meeting.

Step 7. Synthesis of results and quality of the studies: The results and quality of the included studies are synthesized by the Working Group

to provide a summary of the evidence and its quality for each outcome. This synthesis can be narrative or quantitative (for details, see the Instructions for Authors), and the quality synthesis may include use of an overall quality of evidence assessment tool, such as GRADE (Siemieniuk & Guyatt, 2019).

Meta-analyses of large bodies of evidence may be performed by the Working Group and/or by the IARC Secretariat before the meeting if such meta-analyses would assist in evidence synthesis and evaluation. For more information on the conduct and use of such meta-analyses, see Part B, Section 5.1c.

Step 8. Interpretation of study results and evaluation of strength of evidence: The whole Working Group reviews the study descriptions and the summaries of the body of evidence for each outcome or end-point, discusses the overall strengths and limitations of the evidence in each stream of data, and evaluates the strength of evidence for a preventive effect on cancer or an intermediate outcome in each stream using transparent methods, which may include the use of established specific tools. The preventive effect for each stream of evidence is assessed. The Working Group then integrates the assessments from all streams of evidence (see Part B, Section 7.1) and develops the rationale for its consensus evaluation of the preventive effect of the screening or early diagnosis method (see Part B, Section 7.2).

7. Responsibilities of the Working Group

The Working Group is responsible for the final list of studies included in the evaluation and the review and evaluation of the evidence for a *Handbook*, as described above. The IARC Secretariat supports these activities (see Part A, Section 4). To ensure that the process is rigorous, independent, and free from individual conflicts of interest, Working Group members must accept the following responsibilities:

(i) Before the meeting, Working Group members:

- help in developing the analytical framework;
- ascertain that all appropriate studies have been identified and selected;
- assess the methods and quality of each included study;
- prepare pre-meeting drafts that present an accurate quantitative and/or textual synthesis of the body of evidence, with key elements of study design and results and notable strengths and limitations;
- participate in conference calls organized by the IARC Secretariat to coordinate the development of pre-meeting drafts and to discuss cross-cutting issues; and
- review and provide comments on pre-meeting drafts prepared by other members of their Subgroup or of the Working Group.

(ii) At the meeting, Working Group members work in Subgroups to:

- critically review, discuss, and revise the pre-meeting drafts and adopt the revised versions as consensus Subgroup drafts; and
- develop and propose an evaluation of the strength of the evidence summarized in the consensus Subgroup drafts (see Part B, Section 6), using the *IARC Handbooks* criteria (see Part B, Section 7.1).

(iii) At the meeting, Working Group members work in plenary sessions to:

- present their Subgroup drafts for scientific review by and discussion with the other Working Group members, and subsequent revisions, as needed;

- participate in review and discussion of other Subgroup drafts and in their adoption as a consensus Working Group draft;
- participate in review and discussion of the summaries and evaluations of the strength of the evidence developed in Subgroups (see Part B, Section 7.1), and contribute to their revision, as needed, and their adoption by consensus of the full Working Group; and
- contribute to the discussion of and adoption by consensus of an overall evaluation proposed by the Meeting Chair using the guidance provided in Part B, Section 7.1.

The Working Group strives to achieve consensus evaluations. Consensus reflects broad agreement among the Working Group members, but not necessarily unanimity. If unanimity has not been reached when the interpretations of the evidence by all Working Group members have been expressed and debated, the judgement of the majority of the Working Group members is taken as the consensus. When consensus is reached in this way, the Meeting Chair may poll Working Group members to determine and record the diversity of scientific opinion on the overall evaluation.

Only the final product of the plenary sessions represents the views and expert opinions of the Working Group. The *Handbook* is the joint product of the Working Group and represents an extensive and thorough peer review of the body of evidence (review of individual studies, synthesis, and evaluation) by a multidisciplinary group of experts. Initial pre-meeting drafts and subsequent revisions are temporarily archived but are not released, because they would give an incomplete and possibly misleading impression of the consensus developed by the Working Group over its complete deliberation.

B. SCIENTIFIC REVIEW AND EVALUATION

This part of the Preamble discusses the types of evidence that are considered and summarized in each section of a *Handbook*, followed by the scientific criteria that guide the evaluations. In addition, a section of General Remarks at the front of the volume discusses the reasons the interventions were scheduled for evaluation and any key issues encountered during the meeting.

1. Definitions

Secondary prevention of cancer is the use of methods that can lead to the detection of asymptomatic or early symptomatic precancerous conditions or cancers at a stage when treatment of a lesion that is found can prevent progression to invasive cancer or, if the cancer is already invasive, prevent death from cancer. The two cornerstones of secondary prevention are screening and early diagnosis. WHO defines these terms as follows (https://www.who.int/cancer/prevention/diagnosis-screening/en/).

Screening is "the systematic application of a screening test in a presumably asymptomatic population. It aims to identify individuals with an abnormality suggestive of a specific cancer. These individuals require further investigation."

Early diagnosis is "the early identification of cancer in patients who have symptoms of the disease". Early diagnosis is most commonly achieved by raising "the awareness (by the public or health professionals) of early signs and symptoms of cancer in order to facilitate diagnosis before the disease becomes advanced. This enables more effective and simpler therapy."

WHO defines a cancer **early detection programme** as "the organized and systematic implementation of early diagnosis or screening (or both), diagnosis, treatment, and follow-up", thus encompassing both screening and early diagnosis. Early detection programmes, when implemented, usually operate alongside opportunistic early diagnosis and/or screening.

IARC defines an **organized screening programme** as one that has "an explicit policy with specified age categories, method, and interval for screening; a defined target population; a management team responsible for implementation; a health-care team for decisions and care; a quality assurance structure; and a method for identifying cancer occurrence in the target population" (IARC, 2005). In principle, an organized screening programme also includes systematic invitation of the target population for quality-assured screening tests and assured follow-up of screen-positive subjects with diagnostic investigations, treatment, and post-treatment care. The former can minimize inequalities in access to screening by giving every eligible and contactable person access to screening.

Opportunistic refers to the fact that the medical examination is requested by a patient or offered by a health practitioner in the context of the patient–practitioner relationship and is not, or is minimally, subject to any other organizing principle. The proportion of screening for a particular cancer that is opportunistic varies widely from country to country; in many countries screening is exclusively opportunistic, and in some countries screening is almost exclusively organized (for particular types of cancer).

Compared with opportunistic screening, organized screening focuses much greater attention on higher coverage by way of systematic invitation and on the quality of the screening process, and provides greater protection against the harms of screening, including overscreening, poor-quality screening, adverse events of screening, and poor follow-up of those who test positive (Miles et al., 2004). The *IARC Handbooks* assess all available relevant evidence from both organized programmes and opportunistic settings in their evaluation of the effectiveness of a screening method or early diagnosis method.

Whether organized or opportunistic, screening is a complex public health strategy that requires substantial health-care resources, infrastructure, and coordination to be effective. In addition, screening should be undertaken only when efficacy and, ideally, effectiveness have been established. It should also only be undertaken when resources are sufficient to cover a large proportion of the intended target group, when facilities exist for follow-up of screen-positive subjects to confirm or exclude disease and ensure treatment, and where the disease is a sufficiently burdensome public health problem to justify the effort and costs of screening. In addition, information systems are essential to monitor inputs and evaluate outcomes.

Early diagnosis programmes of cancer also have minimum requirements, specifically the facilities needed to confirm or exclude a diagnosis of cancer in people who present to health-care providers with symptoms suggestive of a potentially curable cancer, and to ensure treatment when a diagnosis of cancer is confirmed. At present, the tools of early diagnosis are largely limited to community education about symptoms that may suggest cancer, and to educating or enabling primary care practitioners to ask at-risk patients presenting for *any* care about symptoms they have that may be signs of cancer. Evidence of the effectiveness of such measures is accumulating (Emery et al., 2014). Other possible interventions to promote early diagnosis may involve regulation of health care and organization of health services.

It is important to note that in low- and middle-income countries, depending on societal prioritization, early diagnosis programmes may be the only affordable option for increasing the detection of cancer when it is potentially

curable. Screening (organized or opportunistic) may be unaffordable, although simulation of realistic cost–effectiveness (taking into account all societal costs) might make some programmes attractive.

Early diagnosis and screening are the early parts of a multistep process. The *Handbooks* consider for evaluation the methods used for early diagnosis and screening, and not the steps that follow in the process. Although the following details about the scientific review and evaluation refer specifically to screening interventions, they will also apply for the evaluation of early diagnosis interventions, with some adaptation as needed.

2. Characterization of the disease

This type of *Handbook* addresses screening for cancer at one specific site. Information is presented on the precursor or invasive lesions that cancer screening aims to detect. Each cancer or other lesion is precisely defined as to its location and morphology, using the appropriate codes from the latest International Classification of Diseases for Oncology ([IARC, 2019a](#)) and brief pathological criteria for its diagnosis as published by IARC ([IARC, 2019b](#)). The global distribution and burden of the cancer are summarized, including regional differences, time trends, and credible projections of incidence and/or mortality, based on IARC's data from cancer registries. The natural history of the cancer and its established risk factors and preventive factors are briefly described. The nature and efficacy of evidence-based, potentially curative therapy is also briefly described, together with geographical variation in its nature and accessibility worldwide.

3. Screening methods

Screening methods for the relevant cancer site are considered for evaluation if they have been subject to one or more well-conducted randomized controlled trials with cancer incidence and/or mortality (see Part A, Section 3) as the trial outcome. Screening methods for which no randomized controlled trials are available may be evaluated if the body of evidence from observational studies is sufficiently large to warrant evaluation, especially for screening methods that are already in use in the community.

New screening methods and innovations in existing methods that may offer significant improvements in screening performance, increases in acceptability of screening, or reductions in cost of screening but that did not meet the threshold for detailed review and evaluation described above (i.e. are materially different from other methods under consideration and have not been subject to one or more well-conducted randomized controlled trials or are in widespread use in some countries), or for which the body of evidence was too limited to enable an evaluation to be performed, are also reviewed. The review includes a description and critical assessment of any studies on the performance or the screening effect of these new methods or innovations of existing methods.

Emerging methods may be evaluated in the absence of studies of efficacy or effectiveness if comparative data with an established screening method are available. Such comparative data may include data

(i) on performance against validated reference standards (including those of the International Organization for Standardization [ISO] when relevant);

(ii) on other performance characteristics in populations at average risk; and

(iii) on intermediate outcomes that provide data on efficacy or effectiveness (e.g. sensitivity,

specificity, and interval cancer rate) ([Young et al., 2016](#)).

Ideally, such comparisons will have been made under conditions in which potential biases have been minimized. Possible differences in other important characteristics, such as acceptability and possibility of harm, are also taken into account.

Each method considered for evaluation is described, and its **state-of-the-art application** is outlined. The description of each method should include whether the goal of screening is to reduce cancer-specific mortality by primarily detecting invasive lesions, or to reduce cancer-specific incidence by primarily detecting precursor lesions. The characteristics of the target population, such as age ranges and sex, should be stated. Other relevant issues for the method should be addressed, including:

- equipment and training required;
- technical quality control;
- the screening protocol and its expected performance, including sensitivity and specificity;
- host factors that affect screening performance;
- any assessment protocol for screen-positive subjects; and
- quality assurance.

4. Current global screening practices

A brief overview of relevant screening practices in different regions of the world is presented, limiting the description to those countries or settings where screening takes place. The following aspects are summarized if available:

- policies and guidelines for, and regulation of, screening;

- the type of screening offered (e.g. opportunistic screening, organized population-wide programme);
- the screening methods most commonly used or recommended; and
- availability of facilities, extent of population coverage, and participation rates.

In addition, demographic, cultural, and behavioural considerations that affect participation in screening are presented in a global perspective, with some specific, local characteristics, as appropriate.

5. Epidemiological studies of each screening method

The evaluative processes described here are repeated in full, as far as they apply, for each screening method reviewed.

Relevant studies of cancer in humans are identified using systematic review principles, as described in Part A and further detailed in the Instructions for Authors provided to each Working Group. Eligible studies include: all studies in humans of the association of the screening intervention of interest with its cancer incidence, mortality, or intermediate outcome target (studies of benign neoplasms, pre-neoplastic lesions, and other outcomes are reviewed when they are outcomes sought by, or intermediate outcomes related to, the screening intervention reviewed); studies dealing with the accuracy (sensitivity, specificity, and predictive values) of the screening intervention; studies examining a putative harm as an outcome of the screening intervention; reports on the balance of benefits and harms of screening; and reports on the cost–effectiveness of screening. Search strategies must take into account the possibility that any of the above-mentioned outputs from a single study may have been published separately from the other outputs of the study. Multiple publications may arise from successive follow-ups of a single

trial population or cohort, from analyses focused on different aspects of a screening–outcome association, or from inclusion of overlapping populations. In these situations, only the most recent publication or the one that provides the most, or most relevant, information should be included, unless circumstances warrant otherwise.

5.1 Evaluation of the preventive and harmful effects of the intervention

(a) Types of studies considered

Several types of epidemiological studies contribute to the evaluation of the benefits and harms of cancer screening. Benefits are the principal focus of this section.

(i) *Experimental studies:* Allocation by the investigator of the participants to the intervention (screening) or control condition, ideally by a random and blind process (to the investigator and the participant), is the defining characteristic of experimental studies. These studies can include classic individually randomized controlled trials, cluster-randomized controlled trials that include sufficient clusters to minimize probability of bias, and a range of other designs in which there is non-random allocation of participants to the intervention or control condition or there are too few randomization units to minimize bias.

In principle, experimental studies can provide evidence for efficacy or effectiveness of an intervention that is at low risk of bias. In particular, pragmatic trials (trials designed to test the effectiveness of the intervention in a broad routine clinical practice) can provide evidence of effectiveness when conducted in settings with populations at average risk.

Studies with a tandem design (i.e. the same population is screened with both methods consecutively) can also be useful, to assess an emerging method and its relative impact on screening outcomes.

(ii) *Observational studies:* Typically, observational studies include cohort studies (including variants such as case–cohort and nested case–control studies), case–control studies, cross-sectional studies, and ecological studies, all with cancer incidence or mortality as an outcome. In addition to these designs, innovations in epidemiology enable many variant designs that may be considered in *Handbooks* evaluations. Observational studies generally provide evidence of effectiveness only.

Cohort and case–control studies of screening typically relate individual exposure to the screening intervention under study to the incidence of or mortality from the target cancer in individuals, and provide an estimate of the relative incidence of or mortality from cancer as the main measure of screening effect. In addition, cross-sectional studies may be used to measure accuracy, such as sensitivity, specificity, and predictive values.

In ecological studies, the unit of investigation is not an individual but a whole population or a set of subgroups of a population, and cancer incidence or mortality is related to a summary measure of the exposure (screening method) of the whole population at different times, or aggregate measures of the exposure in the subgroups at the same time. Time-based ecological studies may be of particular interest in evaluating the impact of screening methods, because changes in cancer incidence or mortality, or harms, over interrupted time periods can be related to exposure to the screening method within a single population. Nevertheless, results from ecological studies should be interpreted with caution for two reasons: (i) because they are prone to misclassification of exposure within individual time or population units, due to the lack of individual data on exposure or outcome, and (ii) because

of the limited ability to adjust for confounders. Therefore, ecological studies should generally be used to raise hypotheses and to support the evidence of results from experimental or other observational studies.

(b)   Study quality and informativeness

The following paragraphs outline the general principles of description, analysis, and interpretation of epidemiological studies in a cancer screening context. It is important to note that the evaluation of cancer screening studies involves complexities that are uncommon to other fields of epidemiology. Some examples of these complexities are self-selection for screening, heterogeneity of opportunity to be screened, confounding with differential treatment, and the complexities of lead time, length sampling, and overdiagnosis (IARC, 2016b).

Epidemiological studies are susceptible to several different sources of error. Study quality is assessed as part of the structured expert review process undertaken by the Working Group. A key aspect of quality assessment is consideration of the possible roles of chance and bias in the interpretation of epidemiological studies.

Chance, also called "random variation", can produce misleading study results. This variability in study results is strongly influenced by the sample size: smaller studies are more likely than larger studies to have effect estimates that are imprecise and, therefore, are more likely to be misleading. Confidence intervals around a study's point estimate of effect are routinely used to indicate the range of values of the estimate that could be produced by chance. Both experimental and observational epidemiological studies are prone to effects of chance.

Bias is the effect of factors in study design, conduct, or reporting that lead an association to erroneously appear stronger than, weaker than, or opposite in direction to the association that really exists between an exposure and an outcome. Biases that require consideration are varied and can be broadly categorized as selection bias, information bias (e.g. screening intervention and outcome measurement error), and confounding bias (Rothman et al., 2008). Selection bias in an epidemiological study can occur when the inclusion of participants from the eligible population or their follow-up in the study is influenced by their exposure (screening use) or their outcome (usually disease occurrence). Under these conditions, the measure of association found or not found in the study may not accurately reflect the association or lack thereof that might otherwise have been found in the eligible population (Hernán et al., 2004). Information bias results from inaccuracy in intervention or outcome measurement. Both can cause an association between hypothesized cause and effect to appear stronger or weaker than it really is. Confounding arises when a third factor is associated with both the intervention and the outcome and, because of this, influences the apparent association between them (Rothman et al., 2008). An association between the purportedly preventive intervention and another factor that is associated with an increase or a decrease in the incidence of or mortality from the disease can lead to a spurious association or the absence of a real association of the purportedly preventive intervention with the disease. When either of these occurs, confounding is present.

In principle, experimental studies are less prone to each of these sources of bias, because selection for intervention or non-intervention is determined by the investigator (usually by random allocation) and not by the study participants or their characteristics. However, bias may arise because of lack of concealment, non-random allocation, lack of blinding, post-randomization exclusions, or non-acceptance of or non-adherence by the study participants to the conditions of the study arm (screening or not screening) to which they were randomized when, as is usual in experimental studies of cancer screening, they are not blind to their study arm. In addition,

even when they are blind to the study arm, a high degree of participant non-adherence may cause important information bias and potential confounding with variables related to the choice of whether to adhere or not adhere to the study conditions. Because of such possibilities for confounding, it is common practice to include key confounding variables in the data collected from or about participants, to enable statistical control of confounding.

Two other sources of bias may have important effects on the estimates of the screening efficacy: lead-time bias and length bias (Cole and Morrison, 1980; IARC, 2016b). Lead time is the period between screen detection and when a tumour would have been clinically diagnosed in the absence of screening. The survival time, defined as the time from the date of diagnosis of cancer to the date of death, of screen-detected cases is overestimated because of this lead time, even for individuals who do not benefit from screening. Therefore, lead-time bias can produce data that appear to support a favourable effect of screening, if conclusions are based on survival analysis.

The other important bias is length bias (or length-sampling bias). The probability of a tumour being detected at screening depends, at least in part, on its growth rate, because slow-growing tumours have a longer preclinical detectable phase compared with fast-growing tumours. Thus, tumours detected at screening are a biased sample of preclinical lesions, weighted towards slower-growing tumours, which are generally thought to be associated with a better prognosis and therefore longer survival. This again leads to bias apparently in favour of screening.

In assessing the quality of the studies, the Working Group considers the following aspects:

- **Study description:** Clarity in describing the study design and its implementation, and the completeness of reporting of all other key information about the study and its results.

- **Study population:** Whether the study population was appropriate for evaluating the association between the screening intervention and cancer. Whether the study was designed and conducted in a manner that would minimize selection bias and other forms of bias. The designated outcomes in the study population must have been identified in a way that was independent of the screening intervention, for both experimental studies and observational studies, and the screening intervention must have been assessed in a way that was not related to disease (outcome) status. In these respects, completeness of recruitment into the study from the population of interest and completeness of follow-up for the outcome (see below) are very important.

- **Outcome measurement:** The appropriateness of the outcome measure (incidence of cancer, mortality from cancer, or an intermediate outcome, as defined in Part B, Section 1) for the screening intervention and the cancer type under consideration, the outcome ascertainment methodology, and the extent to which outcome misclassification may have led to bias in the measure or measures of association (e.g. because of systematic differences between exposed and unexposed people in the way in which the outcome was ascertained, and lack of blinding of ascertainment of cancer outcomes, which requires the exercise of human judgement).

- **Intervention measurement:** This includes (i) the adequacy (including the validity and the reliability) of the methods used to assess the intervention in observational studies, and adherence to the intervention condition in experimental studies, and (ii) the likelihood (and direction) of bias in the measure or measures of association because of intervention measurement error or misclassification in observational studies and non-adherence to the intervention condition

and cross-contamination of the non-intervention group in experimental studies (as described in Part B, Section 5.1).

- **Assessment of potential confounding:** The extent to which the authors took into account in the study design and analysis potentially confounding variables, including co-exposures, that could influence the occurrence of the outcome and may be related to the intervention of interest. Particular to screening interventions is the possibility that for a given stage, people with screen-detected cancers receive better treatment than those with symptom-detected cancers. Important sources of potential confounding by such variables should, where possible, have been addressed in the study design, such as by randomization, matching, or restriction, or in the analysis by statistical adjustment. In some instances, where direct information on confounders is unavailable, use of indirect methods to evaluate the potential impact of confounding on intervention–outcome associations is appropriate (e.g. Axelson & Steenland, 1988; Richardson et al., 2014).

- **Other potential sources of bias:** Each epidemiological study is unique in its study population, its design, its data collection, and, consequently, its potential biases. All possible sources of bias are considered for their possible impact on the results. Several sources of bias have important effects on the estimation of screening efficacy. The possibility of reporting bias (selective reporting of some results) should also be explored.

- **Statistical methodology:** The studies are evaluated for the adequacy of the statistical analysis methods used and their ability to obtain unbiased estimates of intervention–outcome associations, confidence intervals, and test statistics for the significance of measures of association. Appropriateness of methods used to address confounding, including adjusting for matching when necessary and avoiding treatment of probable mediating variables as confounders, is considered. Detailed analyses of cancer risks in relation to summary measures of intervention, such as cumulative exposure to the intervention, or temporal variables, such as age at first intervention or time since first intervention, are reviewed and summarized when available.

For the sake of economy and simplicity, this Preamble refers to the **list of possible sources of error** with the phrase "**chance, bias, and confounding**", but it should be recognized that this phrase encompasses a comprehensive set of concerns pertaining to study quality. These elements of study quality do not constitute and **should not be used as a formal checklist** of indicators of study quality. Rather, the assessment by the Working Group is reported in a narrative way, in the form of comments in square brackets. The **judgement of the experts is critical** in determining **how much weight to assign to different issues** when considering how all these potential sources of error should be integrated and how to rate the potential for error related to each. However, it is important that the **process** undertaken, including the weight given to various studies, be **replicable** and be described in a way that is **transparent** to readers.

- **Study informativeness:** The informativeness of a study is its ability to show a true preventive effect, if one exists, of the intervention on the outcome, and not to show an effect if one does not exist. Key determinants of informativeness include having a study population of sufficient size to obtain precise estimates of effect, sufficient elapsed time from intervention to measurement of outcome for an effect, if present, to be observable, presence of adequate intervention contrast, and relevant and well-defined time windows for intervention and outcome.

(c)   Meta-analyses and pooled analyses

Independent epidemiological studies of the same intervention with a comparatively weak effect or small sample size may produce inconclusive results that are difficult to summarize. Combined analyses of data from multiple studies may increase the precision of estimates. There are two types of combined analysis: (i) meta-analysis, which involves combining summary statistics, such as relative risks from individual studies, and (ii) pooled analysis, which involves a pooled analysis of the raw data from the individual studies (Greenland & O'Rourke, 2008). There are also "umbrella reviews", systematic reviews of multiple meta-analyses, which may be evaluated by the Working Group.

The strengths of combined analyses are increased precision due to increased sample size and, in the case of pooled studies, the opportunity to better control for potential confounders and to explore interactions and modifying effects that may help to explain heterogeneity between studies. A disadvantage of combined analyses is the possible lack of comparability of results from various studies, because of differences in specification of the intervention or the outcome, population characteristics, subject recruitment, data collection procedures, methods of measurement, and effects of unmeasured covariates, which may differ among studies. These differences in study methods and quality can influence the results of both pooled analyses and meta-analyses.

Meta-analyses considered by the Working Group may include high-quality published meta-analyses, updates of such meta-analyses, and new meta-analyses. When published meta-analyses are considered by the Working Group, the conduct and reporting quality of the meta-analyses will be carefully assessed against prior expectations set with reference to items in checklists for published systematic reviews and meta-analyses, such as AMSTAR (AMSTAR, 2017) and/or PRISMA (Moher et al., 2009), with additional checks made of the alignment of the systematic review specifications with those required for the *Handbooks* evaluation, the completeness of coverage of articles relevant to the evaluation compared with those ultimately included in the meta-analysis, and the accuracy of extraction of required data from the results of the individual studies.

Subject to the judgement of the IARC Secretariat and in consultation with the Working Group, the updating of meta-analyses or the conduct of ad hoc meta-analyses may be performed by the Working Group and/or by the IARC Secretariat during preparation for a *Handbooks* meeting, when there are sufficient studies of an intervention–outcome association to aid the Working Group's assessment of the association. When results from both experimental and observational studies are available, any combined analyses should be conducted separately for experimental efficacy studies, experimental effectiveness studies, and observational studies, with consideration given to separate combined analyses of cohort and case–control studies, because of their different propensities to bias. The results of such ad hoc meta-analyses, which are specified in the text of the *Handbook* by presentation in square brackets, may come from the addition of the results of more recent studies to those of published meta-analyses or from de novo meta-analyses. Additional details on the conduct of such ad hoc meta-analyses are provided in the Instructions for Authors.

Irrespective of the source of the information for the meta-analyses and pooled analyses, the criteria for information quality applied are the same as those applied to individual studies. The sources of heterogeneity among the studies contributing to them are carefully considered and the possibility of publication bias evaluated.

(d) Evaluation of new technologies

It is important that a new screening test or method is evaluated before it replaces existing technology. New technology need not be subject to a full controlled trial of efficacy if it is similar enough to the old technology and if the old technology has been shown to reduce cancer incidence or cancer mortality. A new technology is considered similar enough if the method of screening is based on the same principles as the old technology and targets lesions with the same biology. In such instances, instead of a full controlled trial of efficacy, the following are required: (i) adequate analytical and clinical validity of the test in human subjects; (ii) cross-sectional evaluation of diagnostic accuracy of the new method for intermediate outcomes validated in randomized controlled trials or in tandem studies in a screening population at average risk (Young et al., 2016); and (iii) a prospective evaluation over more than one screening round of the comparative performance of the two methods, including participation, detection rates, false-positive rates, interval cancer rates, and the burden and harms of screening (Irwig et al., 2006; Young et al., 2016). In the absence of a reduction in risk of interval cancer, any increase in test sensitivity is probably due to an increase in overdiagnosis (see Section 5.2), which could make the new technology more harmful, rather than more beneficial, than the old technology. If the Working Group decides to make a full evaluation of a new screening method in comparison with an existing screening method that has been established to reduce the incidence of cancer or death from cancer, it does a full systematic review of research evidence relevant to this question, as described in Part A, Section 6.

(e) Considerations in assessing the body of epidemiological evidence

The ability of the body of epidemiological evidence to inform the Working Group about the efficacy or effectiveness of a screening intervention is related to both the quantity and the quality of the evidence. There is no formulaic answer to the question of how many studies are needed from which to draw inferences about the efficacy or effectiveness of a screening intervention, although more than a single study in a single population will almost always be needed.

Experimental and observational studies are to be considered. Randomized controlled trials typically provide the strongest evidence, but observational studies also provide valuable and timely information. For example, observational studies can be done for initial evaluation of proposed screening methods and for evaluation of their effectiveness after dissemination has occurred.

After the quality of individual epidemiological studies has been assessed and the informativeness of the various studies on the association between screening and cancer or an intermediate outcome has been evaluated, the body of evidence is assessed and a consensus scientific judgement is made about the strength of the evidence that the screening method under review reduces the incidence of cancer or death from cancer. In making its judgement, the Working Group considers several aspects of the body of evidence (e.g. Hill, 1965; Rothman et al., 2008; Vandenbroucke et al., 2016).

A strong association (e.g. a large relative risk or a relative risk that is well below 1.0) is more likely to be causal than a weak association, because it is harder for confounding or other biases to create a greater association than the one that is observed. However, it is recognized that estimates of effect of small magnitude do not imply lack of causality and may have a substantial impact on public health if the disease is common or if the

screening intervention is highly feasible and/or widely applicable. Estimates of effects of small magnitude can also contribute useful information to the assessment of screening efficacy or effectiveness if the magnitude of the effect correlates with the level of screening intervention in populations that are differently exposed.

Associations that are consistently observed in several studies of the same design, in studies that use different epidemiological approaches, or under different circumstances of intervention are more likely to indicate screening efficacy or effectiveness than are isolated observations from single studies. If there are inconsistent results among investigations, possible reasons for such inconsistencies are sought (e.g. populations studied, intervention characteristics, measurements of outcomes, differences in study informativeness because of time since initiation of the intervention, screening participation), and their implications for the overall findings are assessed.

Results of studies that are judged to be of high quality and highly informative are given more weight than those of studies that are judged to be methodologically less sound or less informative.

Temporality of the association is also an essential consideration, that is, the intervention must precede the outcome, and by a time period that is sufficiently long for observation of a screening effect to be plausible.

5.2 Harms of screening

Potential harms to individuals that are linked to the screening method under review are also reviewed. Evidence of harm may come from any type of epidemiological study (see Section 5.1a) and may also be reported in studies separately from evidence on the benefits of screening using the same criteria as for preventive effects. Although the *IARC Handbooks* do not formally evaluate the harms associated with screening in the way that is done for the benefits, the review of the evidence of harms aims to be as complete, rigorous, and informative as it is for the evidence of beneficial effects.

Occurrence of screening harms is reviewed and described, and their potential impacts are discussed. The evaluation of harms includes: (i) estimates of rates of false-positive and false-negative findings, overdiagnosis, and overtreatment, which are harms shared by all screening methods; and (ii) estimates of risks of harm intrinsic to the screening method, and not necessarily shared by other methods (e.g. radiation-induced cancer due to radiographic screening). Interval cancers are not considered to be a harm, because they are, in essence, a planned outcome of the frequency with which screening is offered to members of the target population and are balanced against harms that would increase in probability with increasing frequency of screening. However, it is recognized that some interval cancers are a consequence of a false-negative test.

The actual harms of the screening test itself or mediated by the screening-related events listed above include: (i) physical and psychological discomfort due to, and medical complications of, the screening method or further investigation of positive findings and subsequent treatment; (ii) all harmful consequences of overdiagnosis and/or overtreatment of screen-detected cancers, including preclinical cancers, and of precancerous lesions; (iii) unnecessary diagnosis and treatment of overdiagnosed cancers; and (iv) delay in diagnosis, a possibly poorer outcome of the targeted cancer, and feelings of betrayal due to the false reassurance of a false-negative finding.

Overdiagnosis is defined in the *Handbooks* as the diagnosis of a cancer as a result of screening that would never have caused any symptoms or problems if it had not been detected by screening. Screening may also detect a large number of precursors of cancer that would not have progressed to clinical cancer in the person's lifetime. The main concern in such

cases is overtreatment. There are challenges to estimating overdiagnosis, and there are several ways in which it can be estimated, including the excess-incidence approach and the mean-lead-time approach. Estimates can be made from "well-conducted, population-based randomized controlled trials with long follow-up and minimal to no screening in the control group" ([Davies et al., 2018](#)), as well as from statistical modelling and from ecological studies. When there are several plausible estimates of overdiagnosis, results of any combined analyses of these estimates are also reviewed.

The IARC Secretariat, in consultation with the Working Group, may also commission or conduct a meta-analysis of such studies.

5.3 Balance of benefits and harms

A sound estimate of the balance of benefits and harms of a screening programme is important to aid decisions about whether to offer the programme and is most important for people who are deciding whether to participate in the programme. Estimates of the balance of benefits and harms for a particular cancer screening programme usually comprise one estimate of benefit (e.g. number of cancer deaths prevented per 1000 eligible people fully participating in the programme) and several estimates of harm (e.g. number of false-positive screening tests, and number of overdiagnosed cancers, per 1000 eligible people fully participating in the programme). These estimates are usually based on experimental or high-quality observational evaluations (e.g. incidence-based mortality analyses done under optimal circumstances) of the performance of screening methods or programmes. To project estimates of benefits and harms to a steady-state programme operating in a particular general population, modelling is required.

After identification of all published estimates of the balance of benefits and harms expressed in absolute terms (e.g. numbers of beneficial and harmful outcomes per 1000 screened individuals), the Working Group selects those based on the highest-quality evaluative studies of the commonly implemented screening regimens, critically assesses each study, summarizes the results in narrative or tabular format as appropriate, and critically assesses the body of evidence. The Working Group may also propose one or more "best" estimates of the balance of benefits and harms, while noting the limits of applicability of those estimates to settings other than the populations and screening experience from which they were derived.

As noted in Part B, Section 1, the balance of benefits and harms of screening is expected to be more favourable in organized screening programmes than in the case of opportunistic screening. The balance may also differ substantially between specific population subgroups, for example human papillomavirus (HPV)-vaccinated and non-vaccinated women for cervical cancer screening. Major factors that influence the balance of benefits and harms include background cancer risk, life expectancy, sex, and age. Where possible, the Working Group will acknowledge these factors and consider comparing benefits and harms for different population subgroups.

In addition to the balance of benefits and harms, the net benefit of screening (which can be positive or negative) may be estimated in an aggregate manner, for example by calculating the average number of quality-adjusted life years (QALYs) gained or disability-adjusted life years (DALYs) averted as a result of screening. QALYs and DALYs are generic measure of disease burden that include quality and quantity of life in their estimation. Because both are based on estimation of lifetime outcomes and are estimated by modelling, they cannot be estimated directly from trials.

In consultation with the Working Group and when it is feasible and potentially contributory,

the IARC Secretariat may commission or conduct a systematic review of modelling studies that have estimated QALYs gained or DALYs averted from screening, and also modelling studies that have estimated disaggregated measures of benefits or harms. The Working Group will critically appraise the quality of the studies using internationally accepted criteria for good modelling conduct (Caro et al., 2012) and applicable subject-specific quality frameworks for models. High-quality collaborative modelling studies (i.e. studies in which different modelling groups work together using standardized assumptions) will be favourably viewed in considering the overall quality of a particular evaluation. Petitti et al. (2018) provided a checklist for the critical appraisal of collaborative modelling reports specific to cancer screening, which can also be used for the appraisal of single modelling studies. Baseline parameters used and their sources, most particularly the sources of calibration data, and other assumptions made in the absence of relevant baseline data require careful scrutiny. Special attention needs to be paid to the extent to which weights for quality and disability have been incorporated for all relevant phases of screening and management of cancer, and also whether disutility is available for all downstream management pathways after the screening test, and whether these have been modelled in detail or as a single aggregate disutility. Currently, there is a general paucity of evidence to support detailed modelling of disutility for each step involved in screening, triage, diagnosis, surveillance, and treatment (all of which are required to model the detailed impact of a screening programme on QALYs or DALYs). As a result, primary studies may judiciously choose to present aggregate benefits information summarized as life years saved, and these data should be considered very carefully as less prone to issues around the uncertainty inherent in estimation of QALYs or DALYs.

5.4 Cost–effectiveness

For a screening method or programme that is capable of delivering a beneficial outcome, cost–effectiveness is usually expressed as the estimated financial cost of implementing the method or programme per unit of the benefit it delivers, which is most often measured in terms of life years, as QALYs gained or DALYs averted. The ratio of costs to benefits (i.e. level of cost–effectiveness) needed to implement a health service programme varies from country to country, depending principally on the wealth of the country and on who pays (e.g. the government or individual citizens). Therefore, the specific ratio derived from cost–effectiveness analyses from a certain country is usually not generalizable to other countries and settings. However, if there are sufficient (high-quality) analyses from different parts of the world with consistent results on the cost–effectiveness of the screening intervention of interest within their respective settings, qualitative statements can be made about the cost–effectiveness of the screening intervention. Although assessments of cost–effectiveness that account for all costs (e.g. that are not restricted to health service costs) are less frequently done, it is important to note that their perspective may differ markedly from one based on health service costs only. Like the balance of benefits and harms, cost–effectiveness estimates can be markedly different in different population subgroups, depending on background cancer risk, life expectancy, sex, and age, among others. Ideally, the cost–effectiveness analysis should be based on the primary population targeted for screening; incremental analyses can consider the inclusion of additional populations (e.g. extended age range for screening).

Taking a similar approach to that taken for the balance of benefits and harms described above, the IARC Secretariat may commission or conduct a systematic review of published reports of cost–effectiveness analyses. Studies to be included

report on net costs (including upfront costs of screening and downstream costs and savings for follow-up and management of cancers) as well as net benefits, preferably in the form of life years gained, QALYs, or DALYs. Methods for all such studies will include modelling. Where applicable, study quality will be appraised in ways similar to those described in Section 5.1b, with the addition of appraisal against internationally accepted criteria for good conduct of cost–effectiveness analysis, such as the Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses by the Second Panel on Cost-Effectiveness in Health and Medicine (Sanders et al., 2016). Methods, assessment against quality criteria, and results will be tabulated for high-quality studies of commonly implemented screening regimens. To ensure sufficient regional variation in the reports, low-quality cost–effectiveness analyses may also be reported and considered in the overall assessment of cost–effectiveness for regions without high-quality reports. The results do not contribute to the overall evaluation of each screening method but can be used by governments and health services to aid decisions about implementation of screening for which there is sufficient evidence of a screening effect.

5.5 Comparison of effects of separately reviewed screening methods

When two screening methods have been established to reduce cancer incidence or cancer mortality, an evaluation may be conducted of the comparative efficacy or effectiveness of these methods. Studies that compare the effects of screening of two or more different screening methods are reviewed and rigorously assessed. Where possible, a statement is made as to the strength of the evidence that use of one screening method is more efficacious or effective than use of another, together with an evaluation of any comparative data about additional dimensions,

such as screening protocol, acceptability, harms, costs, and equity of access, that can influence the population impact of a screening method.

In the absence of such evidence, the Working Group may critically appraise the commonly advanced reasons for choosing one method over another and the justifications given for them, taking into account all the dimensions listed above.

5.6 Surveillance in populations at increased risk

Screening in people with a personal history of the cancer type subject to screening is not evaluated in the *Handbooks*.

Population subgroups at substantially increased risk of the target cancer(s) are briefly described. Available evidence relating to the effect of screening in any of these populations using any of the separately considered screening methods is systematically reviewed and analysed with the same rigour as evidence in whole populations or populations at average risk, and, where possible, a statement is made as to the strength of the evidence that use of any screening method or particular screening method regimen in the group at high risk is more efficacious or effective than use of any other screening method or regimen. Where possible, the magnitudes of the benefits and the harms of the screening method or regimen in these populations are given.

In the absence of such evidence, the Working Group may critically appraise approaches commonly taken to screening in defined groups at high risk and the justifications that have been given for them.

5.7 Other topics reviewed

Some other topics important to the practice of screening may be reviewed in a *Handbook* by summarizing a representative set of studies. These topics do not contribute to the overall

evaluations of the screening methods. They may include, among others:

(a) Determinants of participation in screening

Given an often large and complex literature, a review of reviews of studies in high-income populations and of individual studies from low- and middle-income countries is performed. Special attention is given to the impact on equity of access to effective screening when assessing the role of barriers and the effectiveness of interventions aimed at promoting participation.

(b) Quality of life

The results of studies on gain or loss in quality of life of participants in screening programmes that add useful information on the value of screening are reviewed. Only a few studies have directly investigated change in quality of life as an outcome of screening programmes. These estimates can be used in health (economic) assessments as disability weights when estimating DALYs, QALYs, and cost–effectiveness. Although the available quality-of-life studies usually address physical, social, and emotional functional abilities and general satisfaction, the assessment of health-related quality of life gained or lost through screening programmes is challenging and is heavily context-dependent.

6. Summary of data reported

Each section or subsection of the *Handbook* is summarized. The cancer type subject to screening and its global burden are described, the screening methods evaluated are identified, and their global use is briefly presented. The results of epidemiological studies addressing the efficacy, effectiveness, and harms of each screening method are also summarized. The overall strengths and limitations of the epidemiological evidence base are highlighted to indicate how the evaluation was reached. Typically, the relative and absolute reductions in incidence and/or mortality in populations adhering to the screening regimen evaluated are presented. Harms of the screening intervention are described, both qualitatively and quantitatively, as the evidence base permits.

Depending on the amount and relevance of the data, the Working Group may also summarize the reviewed evidence for cost–effectiveness, and for any other item that the Working Group considers sufficiently important to note.

7. Evaluation and rationale

Although the following details about the evaluation and rationale refer specifically to screening interventions, they will also apply for the evaluation of early diagnosis interventions, with some adaptation as needed.

Consensus evaluations of the strength of the evidence of a reduction of cancer incidence and/or cancer mortality (preventive effects) in humans of each screening method reviewed are made using transparent criteria and defined descriptive terms (see below). Statements should also be made about the evidence for harms and for the balance of benefits and harms.

Where the evaluation of several cancer screening methods indicates that they can reduce cancer incidence and/or cancer mortality (Group A; see below), the Working Group may also choose to indicate whether the efficacy or effectiveness in reducing cancer incidence and/or cancer mortality and the balance of benefits and harms of one screening method are superior to those of another screening method.

Similarly, the Working Group may choose to evaluate the efficacy or effectiveness of one screening method or protocol implemented in a population at increased risk of the cancer, depending on whether relevant evidence is available.

The framework for these evaluations, described below, may not encompass all factors relevant to a particular evaluation of preventive

efficacy or effectiveness. After considering all relevant scientific findings, the Working Group may exceptionally assign the intervention to a different category than a strict application of the framework would indicate, while providing a clear rationale for such an evaluation.

The wording of these evaluations is the same when inferences about preventive effects are made from the results of studies in which an intermediate outcome, not cancer incidence and/or cancer mortality, was the outcome studied. Such evaluations are made only when a causal association has been established between the intermediate outcome and cancer. A statement to this effect is added.

The evaluation is followed by a description or discussion of harms, with a qualitative and quantitative overall evaluation considered in the light of potential and actual harms.

When there are substantial differences of scientific interpretation among the Working Group members, the overall evaluation will be based on the consensus of the Working Group. A summary of the alternative interpretations may be provided, together with their scientific rationale and an indication of the degree of support for each.

The evaluation categories refer to the strength of the evidence that an intervention can reduce the incidence of cancer or death from cancer; they do not address how strongly or weakly the intervention reduces cancer incidence and/or cancer mortality, if it can. Put another way, they do not address the question "By how much might or does this intervention reduce cancer incidence or cancer mortality in exposed people?"

7.1 Evaluation

On the basis of the principles outlined in Part B, Section 5, the evidence relevant to cancer prevention is classified into one of the following categories:

(i) The cancer screening method *is established to reduce the incidence of cancer of the [target organ]* OR *is established to reduce mortality from cancer of the [target organ]* (Group A)

A causal preventive association between use of the screening method or screening methods and cancer incidence or mortality has been established. That is, a preventive association has been observed consistently in the body of evidence on use of the screening method or methods and cancer incidence or mortality, and chance, bias, and confounding as explanations for the association were ruled out with reasonable confidence.

When the evidence is classified in **Group A**, the evaluation is followed by separate sentences to:

- make a statement as to the screening regimen to which the Working Group considers each evaluation of a screening method applies or applies most strongly, and as to whether or not the effectiveness of that screening method has been established;

- make a statement of what the Working Group considers to be the magnitudes of the benefits and the harms of the screening method, in as nearly comparable terms as possible, for people adhering fully to the screening approach most commonly implemented in practice, and whether or not the benefits outweigh the harms.

(ii) The cancer screening method *may reduce the incidence of cancer of the [target organ]* OR *may reduce mortality from cancer of the [target organ]* (Group B)

A causal preventive association between use of the screening method or methods and cancer incidence or mortality is credible, but chance, bias, or confounding as explanations for the association could not be ruled out with reasonable confidence; OR a causal preventive association between use of the screening method and

incidence of precancer or clinically advanced cancer has been established in the absence of an established association for cancer incidence or mortality, respectively.

When the evidence is classified in **Group B**, a sentence makes a statement as to the screening regimen to which the Working Group considers each evaluation of a screening method (or of closely related methods collectively, when evaluated together) applies or applies most strongly.

(iii) The cancer screening method *is not classifiable as to its capacity to reduce the incidence of cancer of the [target organ]* OR *to reduce mortality from cancer of the [target organ]* (Group C)

The available studies are of insufficient quality, consistency, or statistical precision to enable a conclusion to be drawn about the presence or absence of a causal preventive association between the screening method or methods and cancer incidence or mortality; OR there is some evidence that the screening method or methods has a preventive effect, based on precancer or clinically advanced cancer as outcomes, but not enough to qualify for Group B. The first of the above conditions includes: (a) there are relevant studies available, but all are of poor quality or informativeness; and (b) there are relevant studies available of sufficient quality, but their results are inconsistent or otherwise inconclusive.

(iv) The cancer screening method *may lack the capacity to reduce the incidence of cancer of the [target organ]* OR *to reduce mortality from cancer of the [target organ]* (Group D)

There are several high-quality studies that are mutually consistent in not showing a preventive association between the screening method or methods and the studied cancer at the observed levels of use. The results from these studies alone or combined should have narrow confidence intervals with upper limits above or close to the null value (e.g. a relative risk of 1.0). Chance,

bias, and confounding as explanations for the null results were ruled out with reasonable confidence, and the studies were considered informative. Consistent and substantial evidence that the screening method does not result in diagnosis that is earlier in the natural history of cancer than is observed in the absence of screening OR that cancer-specific survival of cancers detected by screening is no better than that of cancers diagnosed in the absence of screening also provide evidence for lack of cancer prevention from the screening method.

A conclusion that the screening method *may lack the capacity to reduce cancer incidence and/ or cancer mortality* is limited to the screening method or methods evaluated and the populations and life-stages, conditions and levels of screening, and length of observation covered by the available studies. In addition, the possibility of a very small preventive effect at the levels of the intervention studied can never be excluded.

7.2 Rationale

The reasoning that the Working Group uses to reach its evaluation is summarized so that the basis for the evaluation offered is transparent. This section includes concise statements of the principal lines of argument that emerged in the deliberations of the Working Group, the conclusions of the Working Group on the strength of the evidence, an indication of the body of evidence that was pivotal to these conclusions, and an explanation of the reasoning of the Working Group in making the evaluations. Where relevant, it also includes reference to use of an intermediate outcome as an, or the, evaluation outcome.

In the rationale, the Working Group may draw attention to the fact that the evaluations should be interpreted in the light of specific circumstances that vary between countries,

which influence the feasibility of implementation of programmes based on the interventions evaluated.

References

AMSTAR (2017). AMSTAR checklist. Assessing the methodological quality of systematic reviews. Available from: https://amstar.ca/Amstar_Checklist.php, accessed 6 March 2019.

Axelson O, Steenland K (1988). Indirect methods of assessing the effects of tobacco use in occupational studies. *Am J Ind Med*. 13(1):105–18. PMID:3344750 doi:10.1002/ajim.4700130107

Boyle P, Levin B, editors (2008). World cancer report 2008. Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/395.

Caro JJ, Briggs AH, Siebert U, Kuntz KM; ISPOR-SMDM Modeling Good Research Practices Task Force (2012). Modeling good research practices – overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Med Decis Making*. 32(5):667–77. PMID:22990082 doi:10.1177/0272989X12454577

Cochrane AL (1972). Effectiveness and efficiency: random reflections on health services. Nuffield Trust. Available from: https://www.nuffieldtrust.org.uk/research/effectiveness-and-efficiency-random-reflections-on-health-services.

Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. (2005). Transparency in IARC Monographs. *Lancet Oncol*. 6(10):747. doi:10.1016/S1470-2045(05)70380-6

Cogliano VJ, Baan RA, Straif K, Grosse Y, Secretan MB, El Ghissassi F, et al. (2004). The science and practice of carcinogen identification and evaluation. *Environ Health Perspect*. 112(13):1269–74. PMID:15345338 doi:10.1289/ehp.6950

Cole P, Morrison AS (1980). Basic issues in population screening for cancer. *J Natl Cancer Inst*. 64(5):1263–72. PMID:6767876

Davies L, Petitti DB, Martin L, Woo M, Lin JS (2018). Defining, estimating, and communicating overdiagnosis in cancer screening. *Ann Intern Med*. 169(1):36–43. PMID:29946705 doi:10.7326/M18-0694

Emery JD, Gray V, Walter FM, Cheetham S, Croager EJ, Slevin T, et al. (2014). The Improving Rural Cancer Outcomes (IRCO) Trial: a factorial cluster-randomised controlled trial of a complex intervention to reduce time to diagnosis in rural patients with cancer in Western Australia: a study protocol. *BMJ Open*. 4(9):e006156. PMID:25231496 doi:10.1136/bmjopen-2014-006156

Greenland S, O'Rourke K (2008). Meta-analysis. In: Rothman KJ, Greenland S, editors. Modern epidemiology. Philadelphia, PA, USA: Wolters Kluwer Health/Lippincott Williams & Wilkins; pp. 652–82.

Hernán MA, Hernández-Díaz S, Robins JM (2004). A structural approach to selection bias. *Epidemiology*. 15(5):615–25. PMID:15308962 doi:10.1097/01.ede.0000135174.63482.43

Hill AB (1965). The environment and disease: association or causation? *Proc R Soc Med*. 58:295–300. PMID:14283879

IARC (1997). Non-steroidal anti-inflammatory drugs. *IARC Handb Cancer Prev*. 1:1–202. Available from: https://publications.iarc.fr/371.

IARC (2002a). Weight control and physical activity. *IARC Handb Cancer Prev*. 6:1–315. Available from: https://publications.iarc.fr/376.

IARC (2002b). Breast cancer screening. *IARC Handb Cancer Prev*. 7:1–229. Available from: https://publications.iarc.fr/377.

IARC (2005). Use of screening for cervical cancer. In: Cervix cancer screening. *IARC Handb Cancer Prev*. 10:117–62. Available from: https://publications.iarc.fr/380.

IARC (2007). Tobacco control: reversal of risk after quitting smoking. *IARC Handb Cancer Prev*. 11:1–358. Available from: https://publications.iarc.fr/381.

IARC (2008). Methods for evaluating tobacco control policies. *IARC Handb Cancer Prev*. 12:1–300. Available from: https://publications.iarc.fr/382.

IARC (2009). Evaluating the effectiveness of smoke-free policies. *IARC Handb Cancer Prev*. 13:1–334. Available from: https://publications.iarc.fr/383.

IARC (2011). Effectiveness of tax and price policies for tobacco control. *IARC Handb Cancer Prev*. 14:1–366. Available from: https://publications.iarc.fr/384.

IARC (2016a). Breast cancer screening. *IARC Handb Cancer Prev*. 15:1–469. Available from: https://publications.iarc.fr/545.

IARC (2016b). Study designs to assess the effectiveness of screening. In: Breast cancer screening. *IARC Handb Cancer Prev*. 15:287–94. Available from: https://publications.iarc.fr/545.

IARC (2018). Guidelines for Observers at *IARC Handbooks* Meetings. Available from: https://handbooks.iarc.fr/preambles/guidelines-for-observers/.

IARC (2019a). International Classification of Diseases for Oncology, ICD-O-3 online. Lyon, France: International Agency for Research on Cancer. Available from: http://codes.iarc.fr/usingicdo.php, accessed 8 January 2019.

IARC (2019b). WHO Classification of Tumours. Lyon, France: International Agency for Research on Cancer. Available from: https://whobluebooks.iarc.fr/, accessed 8 January 2019.

Irwig L, Houssami N, Armstrong B, Glasziou P (2006). Evaluating new screening tests for breast cancer. *BMJ*. 332(7543):678–9. PMID:16565097 doi:10.1136/bmj.332.7543.678

Miles A, Cockburn J, Smith RA, Wardle J (2004). A perspective from countries using organized screening programs. *Cancer*. 101(5 Suppl):1201–13. PMID:15316915 doi:10.1002/cncr.20505

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 6(7):e1000097. PMID:19621072 doi:10.1371/journal.pmed.1000097

Petitti DB, Lin JS, Owens DK, Croswell JM, Feuer EJ (2018). Collaborative modeling: experience of the U.S. Preventive Services Task Force. *Am J Prev Med*. 54(1S1):S53–62. PMID:29254526 doi:10.1016/j.amepre.2017.07.003

Porta M, editor (2008). A dictionary of epidemiology. 5th ed. New York (NY), USA: Oxford University Press. Available from: http://www.oxfordreference.com/view/10.1093/acref/9780195314496.001.0001/acref-9780195314496.

Porta M, editor (2014). A dictionary of epidemiology. 6th ed. New York (NY), USA: Oxford University Press. Available from: https://global.oup.com/academic/product/a-dictionary-of-epidemiology-9780199976737?cc=fr&lang=en&.

Richardson DB, Laurier D, Schubauer-Berigan MK, Tchetgen Tchetgen E, Cole SR (2014). Assessment and indirect adjustment for confounding by smoking in cohort studies using relative hazards models. *Am J Epidemiol*. 180(9):933–40. PMID:25245043 doi:10.1093/aje/kwu211

Rothman KJ, Greenland S, Lash TL (2008). Causation and causal inference. In: Modern epidemiology. Philadelphia (PA), USA: Wolters Kluwer Health/Lippincott Williams & Wilkins; pp. 5–31.

Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. (2016). Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 316(10):1093–103. doi:10.1001/jama.2016.12195 PMID:27623463

Siemieniuk R, Guyatt G (2019). What is GRADE? *BMJ Best Practice*. Available from: https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/, accessed 6 March 2019.

Stewart BW, Kleihues P, editors (2003). World cancer report 2003. Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/397.

Stewart BW, Wild CP, editors (2014). World cancer report 2014. Lyon, France: International Agency for Research on Cancer; Available from: https://publications.iarc.fr/396.

Vandenbroucke JP, Broadbent A, Pearce N (2016). Causality and causal inference in epidemiology: the need for a pluralistic approach. *Int J Epidemiol*. 45(6):1776–86. PMID:26800751 doi:10.1093/ije/dyv341

WHO (2017). Guide to cancer early diagnosis. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/cancer/publications/cancer_early_diagnosis/en/.

Wild CP, Cogliano VJ (2011). A plea on behalf of expert evaluation and the experts involved. *Int J Epidemiol*. 40(1):253–61. PMID:20223796 doi:10.1093/ije/dyq038

Young GP, Senore C, Mandel JS, Allison JE, Atkin WS, Benamouzig R, et al. (2016). Recommendations for a step-wise comparative approach to the evaluation of new screening tests for colorectal cancer. *Cancer*. 122(6):826–39. PMID:26828588 doi:10.1002/cncr.29865

GENERAL REMARKS

WHO initiative

In May 2018, Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organization (WHO), announced a global call to action towards the elimination of cervical cancer, to support and engage countries to scale up evidence-based, cost-effective interventions. In August 2020, the Seventy-third World Health Assembly endorsed the WHO global strategy to accelerate the elimination of cervical cancer as a public health problem 2020–2030 (WHO, 2018, 2020).

WHO guidance for cervical cancer prevention is integral to reaching the United Nations Sustainable Development Goals targets for both health (Goal 3) and gender equality (Goal 5). Meeting the following targets by 2030 will put all countries on the path towards the goal of elimination as a public health problem, which is defined as a threshold of 4 cases of cervical cancer per 100 000 women per year, by 2100:

- 90% of girls fully vaccinated with the human papillomavirus (HPV) vaccine by age 15 years;
- 70% of women screened using a high-performance test by age 35 years and again by age 45 years; and
- 90% of women identified with cervical disease receive treatment (90% of women with

precancer treated, and 90% of women with invasive cancer managed).

In this context, countries are updating their protocols for secondary prevention of cervical cancer. The 2030 cervical cancer elimination targets require up-to-date evidence on screening tests and modalities of screening, as well as new and simpler algorithms for screening and treatment of precancerous lesions that can be implemented at scale.

History of cervical cancer screening

Cervical screening was introduced before the etiology and natural history of cervical cancer were understood, i.e. before the discovery that cervical cancer is caused by a persistent infection with a carcinogenic HPV type. Early cytologists recognized that microscopic signs of invasive cancer, as well as some earlier signs suggesting a less definite probability of cancer, could be found in exfoliated cells (not just in fixed tissue).

The technology of cervical screening based on exfoliated cervical cells was proposed in 1928 by Papanicolaou (Papanicolaou, 1928) and Babeş (Babeş, 1928) and was formally validated in 1941 (Papanicolaou & Traut, 1941). However, it was not until the 1950s and 1960s that cervical screening by cytology (commonly known as Pap

testing) gained a prominent position in primary care. Pap tests reported with the five-level classification system for the probability of cancer became the mainstay of cervical cancer prevention, mostly as an opportunistic intervention in women's primary care visits, initially in the USA and Canada.

In the 1960s, Denmark, Finland, and Sweden, and jurisdictions such as British Columbia in Canada, instituted organized screening programmes for all adult women. Norway started a programme in the 1970s, and England implemented a fully organized programme in the late 1980s (Lăără et al., 1987; Quinn et al., 1999; Safaeian et al., 2007). Throughout the rest of the 20th century, worldwide use of cervical cytology grew, but coverage remained low in resource-limited regions.

Where cytology screening programmes have been established and maintained, they have proven to be successful in reducing the burden of cervical cancer. A successful programme requires high population coverage coupled with technical and programmatic quality assurance. However, because multiple visits and treatments are required in such programmes, they engender high societal cost. This is probably why cervical cytology-based screening programmes have not achieved broad global coverage.

During the 1980s, the central causal role of HPV infection in cervical cancer was established, and the Bethesda system (Solomon, 1989) introduced the category of atypical squamous cells of undetermined significance (ASC-US) (see Sections 1.2.3c and 4.3.1d).

By the mid-1990s, it had been established that persistent infections with certain subtypes of HPV were the necessary cause of almost all cases of cervical cancer. Accordingly, the HPV research community, in collaboration with the nascent HPV testing industry, proposed that only abnormalities that test positive for carcinogenic HPV types should merit referral for colposcopy. Large-scale clinical studies confirmed the

value of such tests, and HPV testing was adopted in some countries as an adjunct test for women with ASC-US. The concurrent advent of liquid-based cytology, which is based on automated processing and production of thin-layer cervical slides, substantially improved the efficiency of Pap smear reading. Liquid-based cytology also enabled HPV testing of women with ASC-US on the same sample.

Although triage of ASC-US-positive women with HPV testing was quickly adopted in several high-resource settings, the usefulness of HPV testing as a primary screening test was immediately evident. Molecular testing for the DNA or RNA of carcinogenic HPV types was shown to have the high sensitivity and throughput required in mass screening. Trials were launched in Europe and North America to compare cytology with HPV testing; they showed the effectiveness of HPV testing in long-term follow-up of studies using multiple rounds of screening.

Detection of one of the carcinogenic HPV types is now established to be the most sensitive test for identifying women at elevated risk of developing cervical precancer and cancer. However, HPV infection is very common and is typically transient. In well-organized settings, follow-up surveillance of women with an HPV-positive test result is used to determine the persistence of the infection; this is the hallmark of an increased risk of cancer. Alternatively, to determine which HPV-positive women are at sufficiently high risk to recommend treatment, a secondary test (triage test) can be performed. Common options for triage are HPV genotyping, cytology (conventional or liquid-based), or colposcopy, and molecular biomarkers are now marketed for this purpose (see Section 4.4.7).

The above-mentioned developments have taken place mainly in high-resource settings. In resource-limited settings, cervical cancer screening based on direct visualization of the cervix, either unaided or aided by magnification or using visualization enhancements with acetic

acid or Lugol's iodine, has been widely used, although without extensive assessment.

Definition of cervical precancer

Cervical screening aims to identify precursors of cervical cancer, thus enabling ablative or excisional treatment to prevent invasive cancer. Therefore, screening is distinguished from stage shifting, which is the diagnosis and treatment of cancer at an earlier stage, to improve the chance of a cure.

The design and evaluation of cervical screening tests and strategies depend on very careful definition of serious precursors that represent true surrogate end-points for risk of invasive cancer. Unless the screening target of precancer is defined accurately and strictly, error is introduced into screening tests and assessments of programme effectiveness.

In this *Handbook*, the Working Group used stringent definitions of precancer, for example by considering only cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) and lesions found in association with carcinogenic HPV types.

Inequalities

The main structural determinant of participation in cervical cancer screening is social inequality in health. Cervical cancer disproportionately affects women of low socioeconomic status who have poor access to screening, diagnosis, and treatment services. Contextual aspects, including education, employment, and social protection policies, act as modifiers or buffers that influence the effects of socioeconomic status on participation (Goss et al., 2013; Yabroff et al., 2020).

Gender inequality, which refers to the differential access of women to structural resources, power, authority, and control, is also a critical determinant of women's capacity to prevent cervical cancer (Kangmennaang et al., 2018). How health-care services are organized and respond to women's needs has been correlated with screening participation. Self-collection of samples for HPV testing has been shown to be effective in increasing screening participation among underscreened women (Arrossi et al., 2015). Therefore, it has great potential to reduce social inequalities in screening, especially if offered in person within the primary health-care system.

Women living with HIV in low-resource settings

Women living with HIV have a higher risk of acquiring HPV, of having persistent HPV infection, and of developing large precancerous lesions, and have a high rate of treatment failure and recurrence of precancer. The natural history of HPV infection in women living with HIV drives the screening and treatment programmes for effective prevention of cervical cancer in women living with HIV in all geographical regions of the world, especially in the regions with the highest prevalence of HIV and incidence of invasive cervical cancer.

Section 5.2.1 of this *Handbook* presents a narrative review of the issues encountered with screening of women living with HIV, mostly in low-resource settings. However, the evaluations are of the effectiveness of the screening methods in the general population, without a particular focus on women living with HIV. For recommendations for screening in this population, the reader is referred to the updated WHO guidelines for screening and treatment of cervical precancer for cervical cancer prevention (WHO, 2021).

Impact of the COVID-19 pandemic on cervical cancer screening

The start of the COVID-19 pandemic, in early 2020, led to a gradual suspension of cancer control activities in most countries. For cervical cancer, screening services were interrupted or scaled down substantially to enable hospitals, clinics, and laboratories to prioritize the health-care needs of patients affected by COVID-19. In addition, with the closing of primary and secondary schools, school-based HPV vaccination was interrupted. Cancer control leaders worldwide have confirmed that reductions in cervical cancer screening activities were dramatic and that coverage of HPV vaccination will return to pre-pandemic levels over time.

The reduced access to screening and vaccination after the reopening of services, which is probably caused by safety concerns, will eventually disappear. As societies reopen and the public regains confidence in resuming health-seeking behaviours, screening and vaccination coverage will return to pre-pandemic levels. However, it is expected that the health-care disruptions that took place in 2020 and beyond will lead to a worsening in the severity of lesions detected on screening in the next few years, and a measurable increase in the incidence of cervical cancer. The most relevant question is: how long will it take for cervical cancer control activities (i.e. screening and vaccination) to reach the planned heightened levels proposed by WHO for the elimination of the disease?

Integration of screening and vaccination in the elimination of cervical cancer as a public health problem

The ambitious goal of eliminating cervical cancer as a public health problem, as adopted by WHO and sanctioned by several countries, is a pressing opportunity. It requires concerted action by all countries, vaccine manufacturers, donor communities, manufacturers of diagnostic tests, and the global health-care community to reach the global targets by 2030. Properly deploying such an ambitious action plan will require the integration of all processes related to HPV vaccination, cervical cancer screening, and clinical treatment and follow-up of all women with precancerous lesions and cancer.

The first 10 years of HPV vaccination programmes have provided evidence on the impact of vaccination with the bivalent or quadrivalent vaccines, which target HPV16 and HPV18. The nonavalent vaccine has been deployed only in the past few years, and therefore its impact has not been ascertained to the same extent as that of the bivalent and quadrivalent vaccines. The impact of the bivalent and quadrivalent vaccines is clear in terms of the decrease in the prevalence of infections with HPV16 and HPV18 and of cervical lesions associated with these HPV types (Pollock et al., 2014; Kavanagh et al., 2017). It is plausible to expect that in the near future the prevalence of lesions caused by HPV types 31, 33, 45, 52, and 58 will also decrease comparably in countries that have introduced the nonavalent vaccine in their programmes. Such additional reductions may be observed towards the end of the 2020s, as the first birth cohorts vaccinated with the nonavalent vaccine become old enough to attend cervical cancer screening.

As the prevalence of cervical precancer decreases further in settings with established screening and vaccination programmes, the clinical utility of high-frequency screening will be questioned, because of the deterioration of the balance of benefits and harms that is inherent in any disease-screening activity. An important challenge for future policy-makers will be the decision to stop screening altogether in settings that maintain only a few screening opportunities during a woman's lifetime (e.g. countries in Europe with organized screening programmes) or to decrease to one or two screens over a lifetime in settings that maintain high-frequency screening (e.g. the USA).

In this regard, a possible decision framework is to use benchmarks of risk tolerance based on screening practices for other cancer types that are rare (Tota et al., 2020). For example, vulvar cancer and vaginal cancer are less common than cervical cancer in the USA today but have relatively poor survival. Although screening would be feasible via cytology and HPV testing for these cancer types, it is not practised and there has never been a proposal for screening. Therefore, the burdens of morbidity and mortality caused by vulvar and vaginal cancers are benchmarks of risk tolerance for inaction in prevention that could assist eventual decisions to stop cervical cancer screening altogether or to decrease to one or two screens over a lifetime (Tota et al., 2020).

References

Arrossi S, Thouyaret L, Herrero R, Campanera A, Magdaleno A, Cuberli M, et al.; EMA Study team (2015). Effect of self-collection of HPV DNA offered by community health workers at home visits on uptake of screening for cervical cancer (the EMA study): a population-based cluster-randomised trial. *Lancet Glob Health*. 3(2):e85–94. doi:10.1016/S2214-109X(14)70354-7 PMID:25617202

Babeş A (1928). Diagnosis of cancer of the uterine cervix by smears. *Presse Med*. 36:451–4.

Goss PE, Lee BL, Badovinac-Crnjevic T, Strasser-Weippl K, Chavarri-Guerra Y, St Louis J, et al. (2013). Planning cancer control in Latin America and the Caribbean. *Lancet Oncol*. 14(5):391–436. doi:10.1016/S1470-2045(13)70048-2 PMID:23628188

Kangmennaang J, Onyango EO, Luginaah I, Elliott SJ (2018). The next Sub Saharan African epidemic? A case study of the determinants of cervical cancer knowledge and screening in Kenya. *Soc Sci Med*. 197:203–12. doi:10.1016/j.socscimed.2017.12.013 PMID:29253722

Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. (2017). Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. *Lancet Infect Dis*. 17(12):1293–302. doi:10.1016/S1473-3099(17)30468-1 PMID:28965955

Lääarä E, Day NE, Hakama M (1987). Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet*. 1(8544):1247–9. doi:10.1016/S0140-6736(87)92695-X PMID:2884378

Papanicolaou GN (1928). New cancer diagnosis. Proceedings of the Third Race Betterment Conference, Battle Creek, Michigan, January 2–6, 1928. Battle Creek (MI), USA: Race Betterment Foundation; pp. 528–534. Available from: doi:10.3322/canjclin.23.3.174

Papanicolaou GN, Traut HF (1941). The diagnostic value of vaginal sears in carcinoma of the uterus. *Am J Obstet Gynecol*. 42:193–206. doi:10.1016/S0002-9378(16)40621-6

Pollock KGJ, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, et al. (2014). Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *Br J Cancer*. 111(9):1824–30. doi:10.1038/bjc.2014.479 PMID:25180766

Quinn M, Babb P, Jones J, Allen E (1999). Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ*. 318(7188):904–8. doi:10.1136/bmj.318.7188.904 PMID:10102852

Safaeian M, Solomon D, Castle PE (2007). Cervical cancer prevention – cervical screening: science in evolution. *Obstet Gynecol Clin North Am*. 34(4):739–60, ix. doi:10.1016/j.ogc.2007.09.004 PMID:18061867

Solomon D (1989). The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. Developed and approved at the National Cancer Institute Workshop, Bethesda, Maryland, U.S.A., December 12–13, 1988. *Acta Cytol*. 33(5):567–74. PMID:2781957

Tota JE, Isidean SD, Franco EL (2020). Defining benchmarks for tolerable risk thresholds in cancer screening: impact of HPV vaccination on the future of cervical cancer screening. *Int J Cancer*. 147(12):3305–12. doi:10.1002/ijc.33178 PMID:32588426

WHO (2018). Executive Board. 144th session. Provisional agenda item 6.5. EB144/28. Accelerating cervical cancer elimination. Report by the Director-General. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/gb/ebwha/pdf_files/EB144/B144_28-en.pdf.

WHO (2020). Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/publications/i/item/9789240014107.

WHO (2021). WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/342365.

Yabroff KR, Reeder-Hayes K, Zhao J, Halpern MT, Lopez AM, Bernal-Mizrachi L, et al. (2020). Health insurance coverage disruptions and cancer care and outcomes: systematic review of published research. *J Natl Cancer Inst*. 112(7):671–87. doi:10.1093/jnci/djaa048 PMID:32337585

LIST OF ABBREVIATIONS

ACA	Affordable Care Act
ACS	American Cancer Society
AGC	atypical glandular cells
AI	artificial intelligence
AIS	adenocarcinoma in situ
ALTS	Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study
ART	antiretroviral therapy
ARTISTIC	A Randomised Trial In Screening To Improve Cytology
ASC	atypical squamous cells
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion
ASC-US	atypical squamous cells of undetermined significance
ASC-US+	atypical squamous cells of undetermined significance or worse
ASIR	age-standardized incidence rate
ASMR	age-standardized mortality rate
ATHENA	Addressing the Need for Advanced HPV Diagnostics
AUC	area under the curve
BIRST	Bethesda Interobserver Reproducibility Study
BMD	borderline or mild dyskaryosis
CASSIS	Cervical And Self-Sample In Screening
CCCaST	Canadian Cervical Cancer Screening Trial
CCPCN	Cervical Cancer Prevention and Control Network
CCPPZ	Cervical Cancer Prevention Program in Zambia
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CIN1	cervical intraepithelial neoplasia grade 1
CIN2	cervical intraepithelial neoplasia grade 2
CIN2+	cervical intraepithelial neoplasia grade 2 or worse
CIN3	cervical intraepithelial neoplasia grade 3
CIN3+	cervical intraepithelial neoplasia grade 3 or worse
CIS	carcinoma in situ
CLEAR	Clinical Evaluation of Aptima mRNA
CNN	convolutional neural network

cNPV	complement of negative predictive value
CPAC	Canadian Partnership Against Cancer
CSQ	Cervical Screening Questionnaire
CYTOTRAIN	Transnational Training Programme in Cervical Cytology
EIA	enzyme immunoassay
EU	European Union
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FSFI	Female Sexual Function Index
GHQ	General Health Questionnaire
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HARP	HPV in Africa Research Partnership
HART	HPV in Addition to Routine Testing
HAT	Hanover and Tübingen
HC2	Hybrid Capture 2
HDI	Human Development Index
HIP	HPV Impact Profile
HIV	human immunodeficiency virus
HPV	human papillomavirus
HPV FOCAL	HPV For Cervical Cancer Screening
HR	hazard ratio
hrHPV	high-risk human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
HSIL+	high-grade squamous intraepithelial lesion or worse
IARC	International Agency for Research on Cancer
ICC	invasive cervical cancer
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
IFCPC	International Federation of Cervical Pathology and Colposcopy
IRR	incidence rate ratio
KPNC	Kaiser Permanente Northern California
LAST	Lower Anogenital Squamous Terminology
LBC	liquid-based cytology
LEEP	loop electrosurgical excision procedure
LEGH	lobular endocervical glandular hyperplasia
LLETZ	large loop excision of the transformation zone
LMICs	low- and middle-income countries
LSIL	low-grade squamous intraepithelial lesion
LSIL+	low-grade squamous intraepithelial lesion or worse
mRNA	messenger RNA
NBCCEDP	National Breast and Cervical Cancer Early Detection Program
NCCSPRA	National Cervical Cancer Screening Program in Rural Areas
NETZ	needle excision of the transformation zone
NGO	nongovernmental organization
NHIC	National Health Insurance Corporation
NHS	National Health Service
NILM	negative for intraepithelial lesion or malignancy
NNCTR	Nepal Network for Cancer Treatment and Research
NPV	negative predictive value
NTCC	New Technologies for Cervical Cancer Screening

OR	odds ratio
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PHE	Public Health England
PHQ4	Patient Health Questionnaire-4
PICOS	population, intervention, comparator, outcome, and studies
POBASCAM	Population Based Screening Study Amsterdam
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCI	Reid Colposcopic Index
RCT	randomized controlled trial
ROC	receiver operating characteristic
RR	relative risk
SAR	Special Administrative Region
SCC	squamous cell carcinoma
SCJ	squamocolumnar junction
SEER	Surveillance, Epidemiology, and End Results
SIL	squamous intraepithelial lesion
SIR	standardized incidence ratio
SPOCCS I	Shanxi Province Cervical Cancer Screening Study I
sROC	summary receiver operating characteristic
STAI	State-Trait Anxiety Inventory
STARD	Standards for Reporting of Diagnostic Accuracy Studies
STEPS	STEPwise approach to Surveillance
SwedeScreen	Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Cancer Screening
SWETZ	straight wire excision of the transformation zone
TBS	the Bethesda system
TNM	tumour–node–metastasis
TOC	test of cure
TOMBOLA	Trial of Management of Borderline and Other Low-grade Abnormal smears
TZ	transformation zone
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNFPA	United Nations Population Fund
UNJGP	United Nations Joint Global Programme on Cervical Cancer Prevention and Control
USPSTF	United States Preventive Services Task Force
VIA	visual inspection with acetic acid
VILI	visual inspection with Lugol's iodine
VUSA-Screen	Vrije Universiteit Medical Centre-Saltro Laboratory Population-Based Cervical Screening
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WLHIV	women living with HIV
WOLPHSCREEN	Wolfsburg Pilot Project for Better Prevention of Cervical Cancer with Primary HPV Screening

GLOSSARY

Background incidence rate	The incidence rate expected in the absence of screening.
Cancer detection rate	The proportion of screening examinations (by any means) in which at least one cancerous lesion is detected.
Cancer incidence rate	The rate at which new cases of cancer occur in a population. The numerator is the number of newly diagnosed cases of cancer that occur in a defined time period. The denominator is the population at risk of a diagnosis of cancer during this defined period, sometimes expressed as person–time at risk during that period.
Cancer mortality rate	The rate at which deaths from cancer occur in a population. The numerator is the number of cancer deaths that occur in a defined time period. The denominator is the population at risk of dying from cancer during this defined period, sometimes expressed as person–time at risk during that period.
Cancer register	A record of information on all new cases of cancer and deaths from cancer that occur in a defined population.
Effectiveness	A measure of the extent to which screening, when deployed in the field under real conditions, does what it is intended to do for a specified population. The most important indicator of the effectiveness of a cervical cancer screening programme is its effect in reducing cervical cancer mortality.
Efficacy	The extent to which screening produces a beneficial result under ideal conditions. Randomized controlled trials, which are conducted to initially assess whether screening works, assess efficacy by estimating a primary outcome, such as reduction in cervical cancer mortality in the study arm compared with the control arm.
Eligible population	The adjusted target population, i.e. the target population minus those people who are excluded according to screening policy on the basis of eligibility criteria other than age, sex, and geographical location.
Examination coverage	The number of people screened with the recommended test in a given year divided by the number of people eligible for screening (the eligible target population per screening interval) in the same reference year.
False positive	A test result indicating that a person has cervical cancer when the person does not have cervical cancer.
Invitation coverage	The number of people invited to screening in a given year divided by the number of people eligible for screening (the eligible target population per screening interval) in the same reference year.
Lead time	The period between when a cancer is found by screening and when it would have been detected from clinical signs and symptoms (not directly observable) in the absence of screening.

Opportunistic screening	Screening outside an organized or population-based screening programme, as a result of, for example, a recommendation made by a health-care provider during a routine medical consultation, during a consultation for an unrelated condition, on the basis of a possibly increased risk of developing cervical cancer (family history or other known risk factor), or by self-referral of individuals. Opportunistic screening relies on individual health-care providers taking the initiative to offer screening or to encourage individuals to participate in a screening programme, or to undertake screening outside the context of any programme. Such examinations can be performed according to the public screening policies, where they exist.
Organized screening programme	A screening programme organized at a national or regional level that has an explicit policy with specified age categories, method, and interval for screening; a defined target population; a management team responsible for implementation; a health-care team for decisions and care; a quality-assurance structure; and a method for identifying cancer occurrence in the target population.
Overdiagnosis	The diagnosis of a cancer as a result of screening that would not have been diagnosed in the patient's lifetime if screening had not taken place.
Overtreatment	The treatment of a lesion that would never have progressed to be clinically recognized during a woman's lifetime.
Participation rate	The number of people screened divided by the eligible number of people invited to screening during the reference period (applies only for organized population-based programmes).
Population-based cancer registry	A registry that systematically collects information from multiple sources on all reportable neoplasms occurring in a geographically defined population, to provide information on cancer burden, assess possible causes of cancer, and carry out studies on prevention, early detection and screening, and cancer care. The registry provides a profile of the cancer burden in the population and how it changes over time, and therefore plays an important role in the planning and evaluation of cancer control programmes.
Population-based screening programme	A screening programme at a national or regional level that has a mechanism to identify the eligible individuals according to the screening policy and to send personal invitations to the eligible individuals to attend screening.
Positive predictive value	The proportion of all positive results at screening that lead to a diagnosis of cancer.
Prevalence	The proportion of a population that exhibit a disease (classified as cases) at a single point in time. Approximately the product of the incidence and the average duration of the disease.
Screen-and-treat approach	A strategy in which individuals with a positive screening test result receive immediate treatment without a colposcopy-directed biopsy and histological confirmation of precancer. Ideally, screening and treatment are performed during the same visit.
Screening interval	The time interval between two screening episodes (rounds), within a screening programme or in an opportunistic setting.
Screening policy	A policy for a specific screening programme that defines the targeted age group and sex group, the geographical area, and other eligibility criteria; the screening test and interval; follow-up strategies; and requirements for payment or co-payment, if applicable. At a minimum, the screening protocol and repeat interval and determinants of eligibility for screening are stated.
Screening programme	Cancer screening performed in the framework of a publicly mandated programme. To be considered a programme, there has to be a commitment from the government to provide the screening services to the eligible population as defined by laws, statutes, regulations, or official notifications. At a minimum, the eligible population, the screening test, and the screening interval should be defined, and there should be some mechanism for monitoring and supervision.
Screening registry	An information system (computerized or paper-based) that collects and stores cancer screening data on individual participants to use for programme management and reporting.
Sensitivity	The proportion of truly diseased persons in the screened population who are identified as diseased by the screening test. The more general expression for "sensitivity of the screening programme" refers to the ratio of true positives (cervical cancers correctly identified at the screening examination) / [true positives + false negatives] (cervical cancers not identified at the screening examination, detected as interval cases).
Specificity	The proportion of truly non-diseased persons in the screened population who are identified as non-diseased by the screening test (i.e. true negatives / [true negatives + false positives]).

Stage shift	A shift to a lower stage of the cancers detected.
Target population	The age-eligible population for screening, for example all women offered screening according to the policy.
WHO African Region	Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eswatini, Eritrea, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Africa, South Sudan, Togo, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.
WHO Eastern Mediterranean Region	Afghanistan, Bahrain, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, West Bank and Gaza Strip, Yemen.
WHO European Region	Albania, Andorra, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Monaco, Montenegro, The Netherlands, North Macedonia, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, United Kingdom, Uzbekistan.
WHO Region of the Americas	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia (Plurinational State of), Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, USA, Venezuela (Bolivarian Republic of).
WHO South-East Asia Region	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste.
WHO Western Pacific Region	Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, Hong Kong Special Administrative Region, Japan, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, New Zealand, Niue, Papua New Guinea, Philippines, Republic of Korea, Samoa, Singapore, Solomon Islands, Taiwan (China), Tonga, Tuvalu, Vanuatu, Viet Nam.

1. CERVICAL CANCER

1.1 Global cervical cancer burden

1.1.1 Incidence

Cervical cancer (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code, C53 – Malignant neoplasm of cervix uteri) is the fourth most commonly diagnosed cancer type in women of all ages worldwide (Sung et al., 2021). In women of reproductive age (15–44 years), it is the second most common cancer type; cervical cancer is the most common cancer in 23 countries, most of which are in sub-Saharan Africa (Ferlay et al., 2020). In 2020, there were an estimated 604 000 new cases worldwide, and cervical cancer represented about 6.5% of the global cancer burden in women; the proportions were higher for only breast cancer (24.2%), colorectal cancer (9.4%), and lung cancer (8.4%). The highest proportion of new cases occurred in Asia (58.2%), followed by Africa (19.4%), Latin America and the Caribbean (9.8%), Europe (9.6%), Northern America (2.5%), and Oceania (0.4%) (Ferlay et al., 2020; Sung et al., 2021).
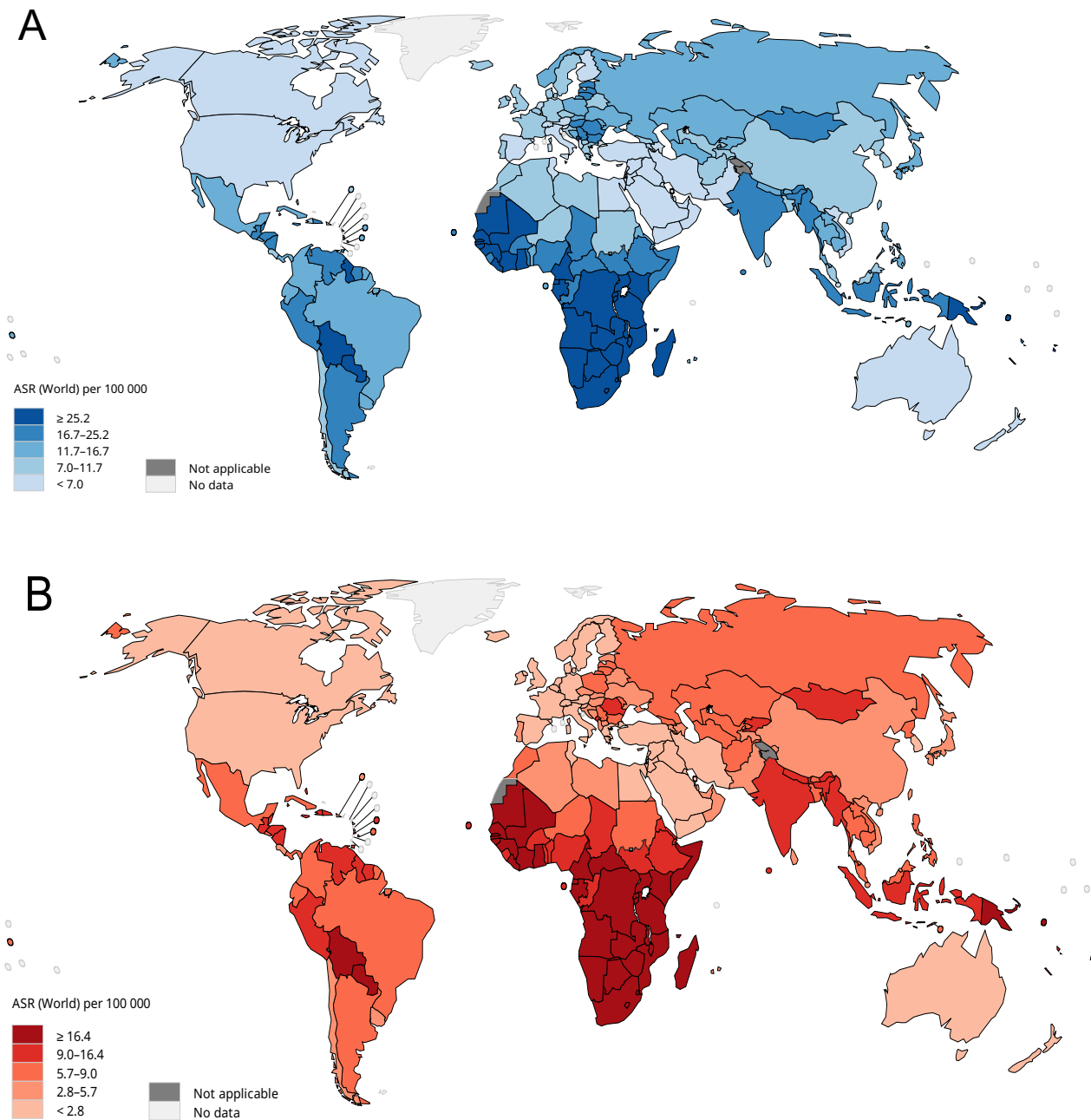
In 2020, the global age-standardized incidence rate (ASIR) of cervical cancer was 13.3 per 100 000 women worldwide (Ferlay et al., 2020). The incidence rates of cervical cancer vary markedly across the world, with a 10-fold variation between the highest and lowest rates

(Fig. 1.1 and Fig. 1.2). The estimated incidence rates (ASIR, per 100 000 women) are highest in Eastern Africa (40.1), Southern Africa (36.4), Middle Africa (31.6), Melanesia (28.3), and Western Africa (22.9), followed by the Federated States of Micronesia (18.7), South-Eastern Asia (17.8), South America (15.4), and South-Central Asia (15.3), and lowest in Western Asia (4.1) and Australia and New Zealand (5.6) (Ferlay et al., 2020; Sung et al., 2021). The incidence rates of cervical cancer are higher in countries that have a high prevalence of HIV infection and/or lack sustained cervical cancer screening programmes (Rohner et al., 2020).
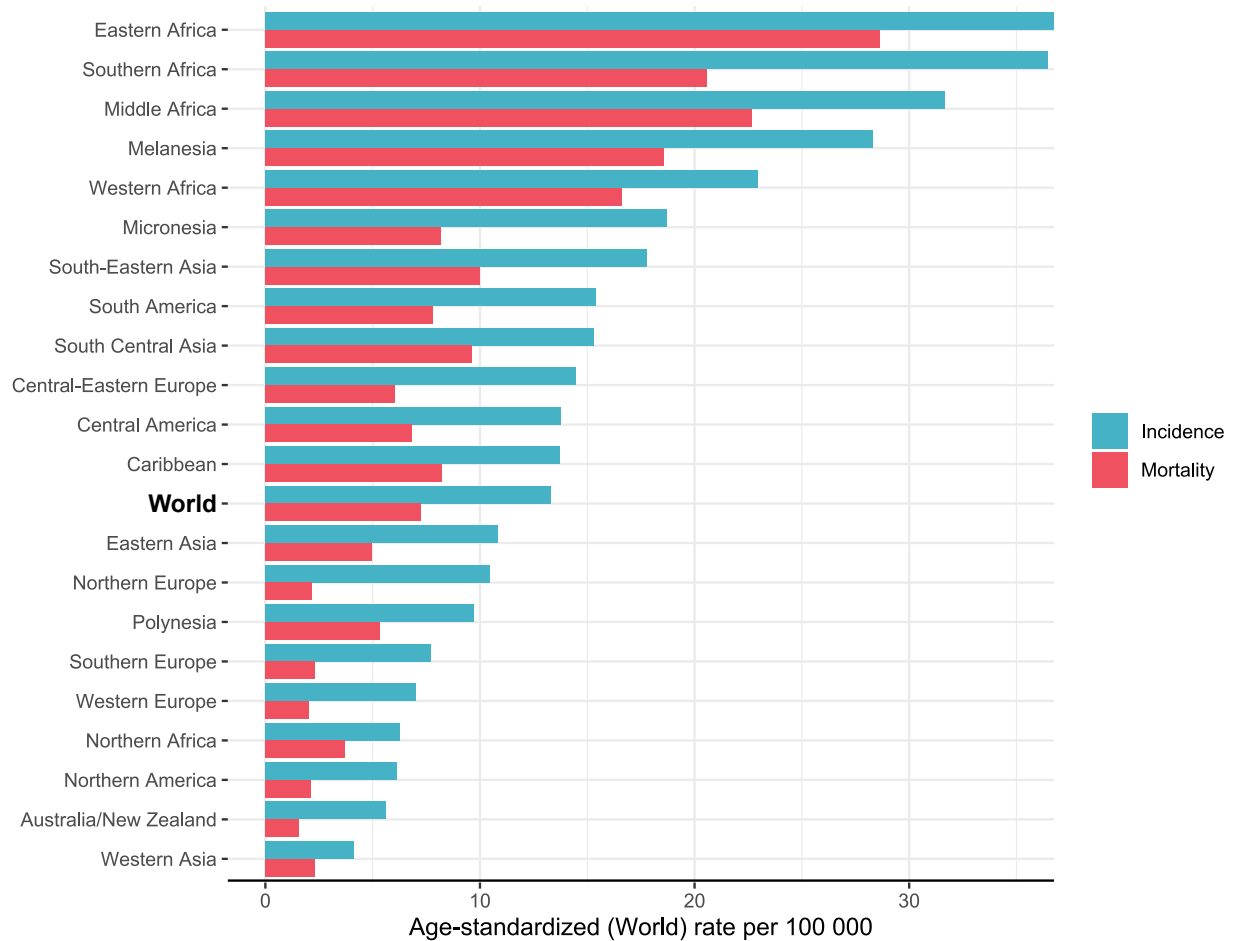
1.1.2 Mortality

Cervical cancer is the fourth most common cause of cancer death in women of all ages, after breast cancer, lung cancer, and colorectal cancer. In women of reproductive age (15–44 years), it is the second most common cause of cancer death (Arbyn et al., 2020). In 2020, there were an estimated 342 000 deaths worldwide due to cervical cancer; the proportion of deaths was highest in Asia (58.5%) and Africa (22.5%), followed by Latin America and the Caribbean (9.2%) and Europe (7.6%), and lowest in Northern America (1.9%) and Oceania (0.4%) (Ferlay et al., 2020; Sung et al., 2021).

Fig. 1.1 Global distribution of estimated age-standardized (World) incidence rates (A) and mortality rates (B) per 100 000 for cervical cancer, 2020

Adapted from Ferlay et al. (2020). Courtesy of Jérôme Vignat.

Fig. 1.2 Estimated age-standardized (World) incidence and mortality rates per 100 000 for cervical cancer, by large world regions, 2020
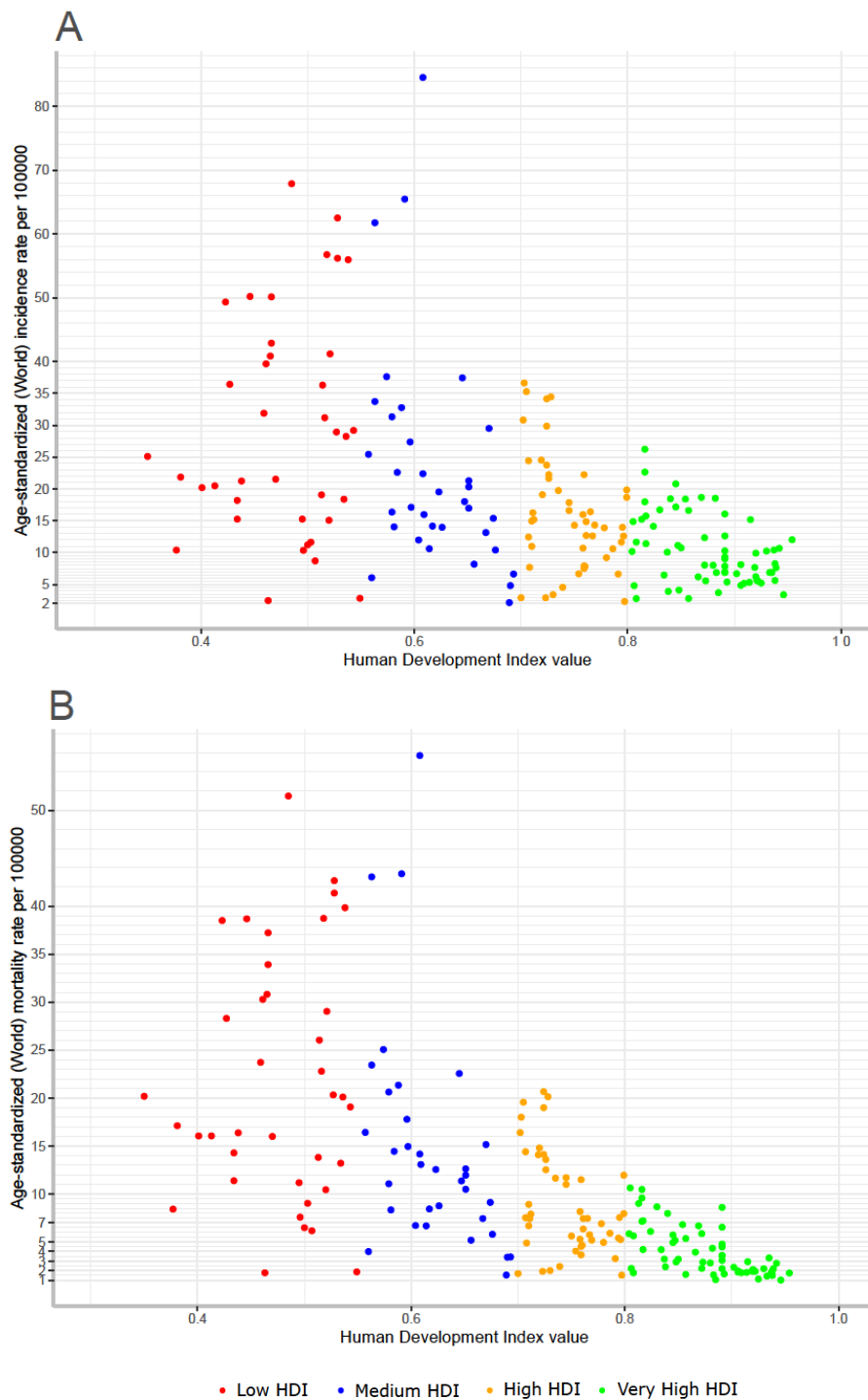

Adapted from Ferlay et al. (2020). Courtesy of Jérôme Vignat.

In 2020, the age-standardized mortality rate (ASMR) for cervical cancer was 7.3 per 100 000 in women worldwide (Ferlay et al., 2020; Sung et al., 2021). The mortality rates of cervical cancer have a global pattern similar to that for the incidence rates, with a more than 15-fold variation between the highest and lowest rates (Fig. 1.1 and Fig. 1.2). The estimated mortality rates (ASMR, per 100 000 women) are highest in Eastern Africa (28.6), Middle Africa (22.7), Southern Africa (20.6), Melanesia (18.6), Western Africa (16.6), South-Eastern Asia (10.0), and

South-Central Asia (9.6), and lowest in Australia and New Zealand (1.6) and Western Europe (2.0) (Ferlay et al., 2020; Sung et al., 2021).

The highest cervical cancer incidence and mortality rates are generally observed in countries with the lowest levels of the Human Development Index (HDI) (Ginsburg et al., 2017) (Fig. 1.3). In countries with lower HDI, the incidence and mortality rates span a wider range, suggesting that other factors besides HDI may account for the variability, such as exposure to human papillomavirus (HPV) or other cofactors

Fig. 1.3 Correlation between estimated age-standardized (World) cervical cancer incidence rates (A) and mortality rates (B) per 100 000 and Human Development Index (HDI), 2020

The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).
Created using data from Ferlay et al. (2020) and UNDP (2020). Courtesy of Jérôme Vignat.

Fig. 1.4 Age-specific incidence of cervical cancer worldwide and in terms of the four-tier Human Development Index (HDI), 2018
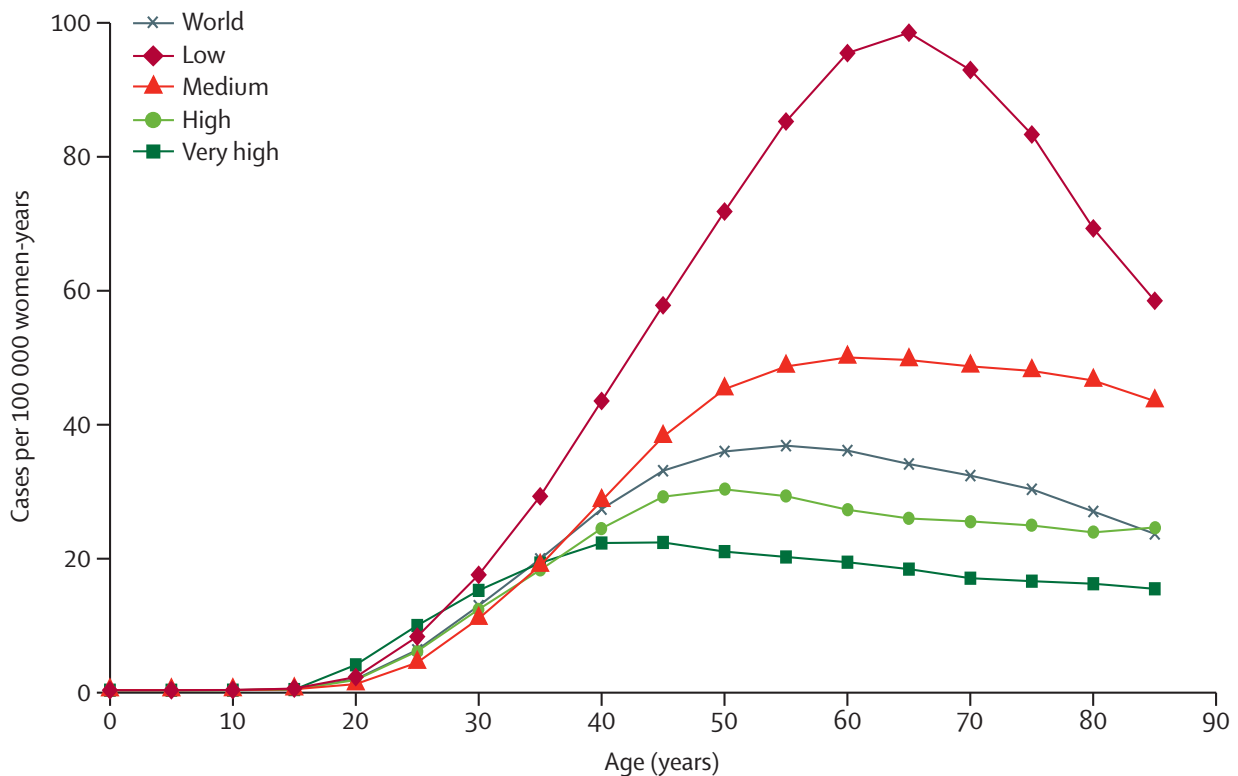
The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).
Reproduced from Arbyn et al. (2020).

or the coverage and type of screening (opportunistic vs organized). In those countries with the highest HDI, both incidence rates and mortality rates are in a narrow range despite similar prevalences of HPV infection or other cofactors. The age-specific incidence rates of cervical cancer are presented in Fig. 1.4. Cervical cancer incidence rates start rising after age 25 years worldwide, but in countries with high and very high HDI, the peak of incidence is reached at about age 40 years, whereas in countries with medium and low HDI, the rate continues to rise until age 55–69 years (Arbyn et al., 2020).

1.1.3 Trends in incidence

An analysis of trends in age-standardized cervical cancer incidence rates over time using the *Cancer Incidence in Five Continents* database (Ferlay et al., 2018) revealed variability in trends across countries and showed how these trends are influenced by a country's context of policy, programmes, practice, and culture. Fig. 1.5 shows overall trends and trends in women younger than 40 years by country in all registries that provided data for the longest period. Trends for women older than 40 years are not presented, because they tend to be very similar to the overall trends. Also, trends in the registries that provided data for the longest period may not represent trends in the whole country. Three patterns emerge

Fig. 1.5 Trends in age-standardized (World) incidence rates for cervical cancer by country
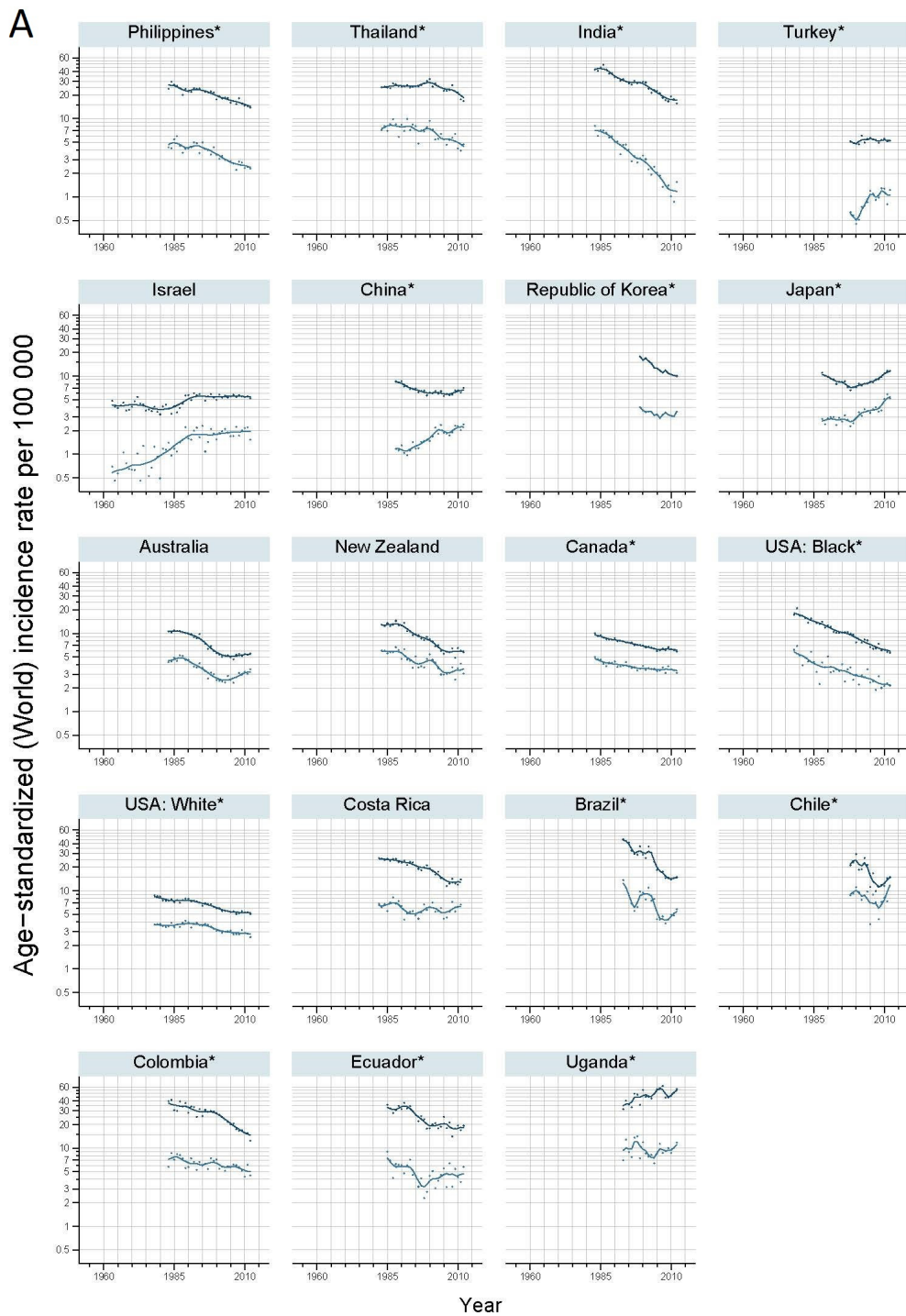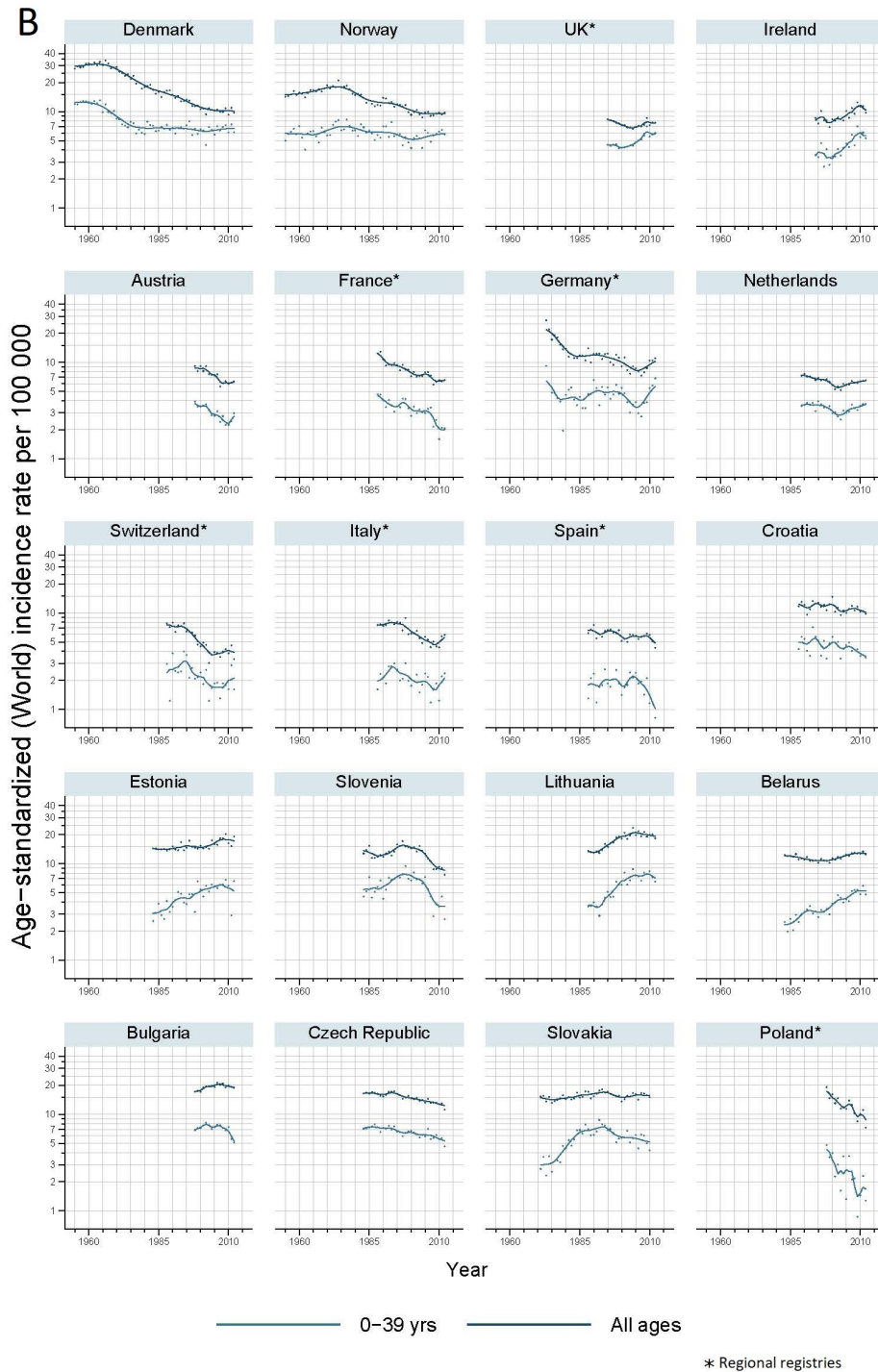
Fig. 1.5 (continued)

(A) For World, countries with fewer than 500 cases have been excluded (Bahrain and Kuwait).
(B) For Europe, countries with fewer than 1000 cases have been excluded (Cyprus, Iceland, and Malta).
Created using data from Ferlay et al. (2018). Courtesy of Jérôme Vignat.

from these trends: (i) a decrease in rates over the years, (ii) an increase in overall rates, and (iii) an increase in rates in the younger age groups.

In most countries, cervical cancer incidence rates have been decreasing over the past decades, although the magnitude of the decrease may vary. In many of these countries, the decrease can be attributed to sustained population-based screening programmes; for example, in Denmark, Finland, Norway, and Sweden, the introduction of screening programmes in the 1960s and 1970s resulted in an almost 50% reduction in cervical cancer incidence. In countries where there is no population-based screening, as for example in India, the decrease in cervical cancer incidence may reflect improved conditions, such as better education for girls and women, which lead to reduced exposure to HPV, among other factors (Dhillon et al., 2011).

The second emerging pattern is a continued increase in incidence rates. In some countries (e.g. Belarus, Estonia, and Lithuania), incidence rates are increasing despite the introduction of screening programmes; this trend reflects weak opportunistic screening, poor coverage of screening, and poor quality (Vaccarella et al., 2016; Ojamaa et al., 2018). In Uganda, which has one of the longest-standing high-quality registries, there has been a continued increase in cervical cancer incidence rates. In a recent analysis of 10 African registries with 10–25 years of data, a similar pattern was seen and was attributed to a high prevalence of HPV infection, a high prevalence of HIV infection, and a lack of well-attended population-based screening programmes (Jedy-Agba et al., 2020).

In the third pattern, the overall trend is decreasing but incidence rates in women younger than 40 years are increasing. Such a pattern has been observed in China, most likely reflecting increased exposure to HPV in the youngest cohort of women (Li et al., 2017).

Trends by histology cannot be provided at a global level, given the lack of histology data in many cancer registries. However, in selected countries the examination of incidence rates by histology provides insights into the impact of prevention strategies. For example, the reduction in the incidence of cervical cancer seen in the USA from the introduction of the Pap test in the 1960s until the early 2000s has been driven by reductions in the incidence rates of squamous cell carcinoma (SCC) of the cervix (Wang et al., 2004). In the past two decades, incidence rates of cervical SCC have stabilized in the USA (Islami et al., 2019), whereas incidence rates of cervical adenocarcinoma have increased both in the USA (especially in White women aged 40–60 years) (Islami et al., 2019) and in Europe (Bray et al., 2005). This trend may reflect changing sexual behaviours over time (Ryser et al., 2017), as well as an inability to detect cervical adenocarcinoma through cytology-based screening programmes (Castle et al., 2017).

1.1.4 Lifetime risk of cervical cancer

The lifetime cumulative risk of cervical cancer for women aged 0–74 years is presented by region in Fig. 1.6. In Africa, the lifetime risk varies from 8.6% in Eswatini to 0.3% in Egypt. In Latin America and the Caribbean, women in the Plurinational State of Bolivia and in Guyana have a lifetime risk of 3.7%, whereas those in Martinique, France, have a lifetime risk of 0.6%. In Asia, the lifetime risk is highest in Maldives, Indonesia, and Mongolia and lowest in Iraq. Women in eastern Europe have consistently higher lifetime risk than those in western Europe (Ferlay et al., 2020; Sung et al., 2021).

1.1.5 Survival

At the end of 2020, there were an estimated 1.5 million women alive who had been diagnosed with cervical cancer during the previous 5 years,

Fig. 1.6 Estimated cumulative risk (ages 0–74 years) of cervical cancer incidence by world region and country or territory, 2020
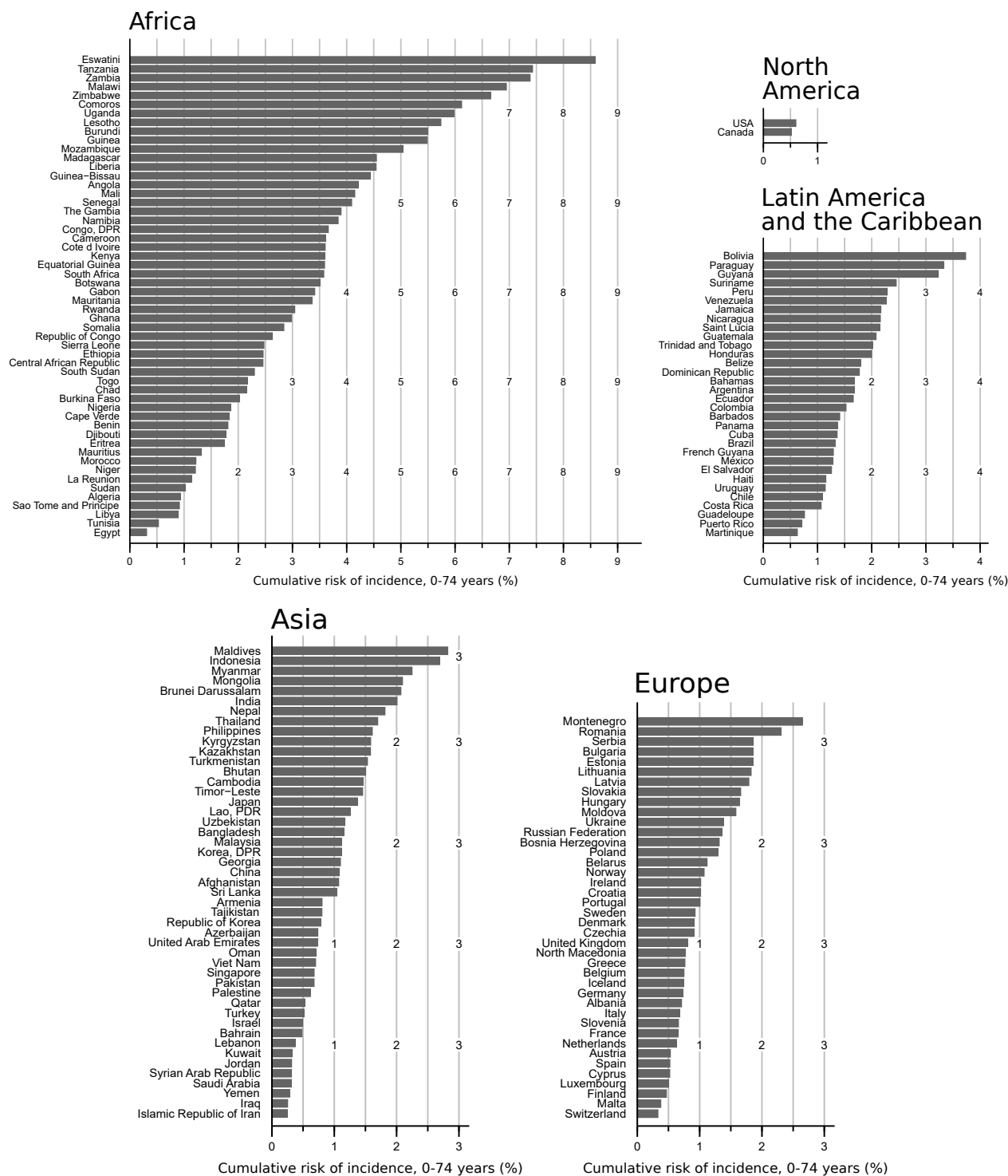
Adapted from Ferlay et al. (2020). Courtesy of Mathieu Laversanne.

representing about 5.8% of all people who were diagnosed with cancer within the previous 5 years (Ferlay et al., 2020).

The third cycle of the CONCORD programme for global surveillance of cancer survival trends (CONCORD-3) included data for 660 744 women diagnosed with cervical cancer in 2000–2014 from 295 population-based cancer registries in 64 countries or territories. Population-based survival is estimated from data provided by population-based cancer registries that record all diagnoses of malignancy in the population of the country or region that they cover. It is a key measure of the overall effectiveness of the health system in managing cancer in a given country or region (Allemani, 2017; Allemani et al., 2018).

Population-based survival is a measure of the average survival of all patients with cancer. Population-based survival is usually presented as net survival (Perme et al., 2012), which is the probability of patients with cancer surviving until a given time since diagnosis, typically 5 years, after controlling for competing causes of death (background mortality).

The global range in 5-year age-standardized net survival for cervical cancer was wide (50–70%) in all three calendar periods (2000–2004, 2005–2009, 2010–2014), reflecting inequity in access to diagnostic facilities and optimal treatment (Allemani et al., 2018). For women diagnosed in 2010–2014, 5-year age-standardized net survival was 70% or higher in seven countries or territories (Cuba; Denmark; Japan; Norway; the Republic of Korea; Switzerland; and Taiwan, China), most of which have high HDI. Survival was in the range 60–69% in 29 countries or territories: Canada and the USA; Brazil and Puerto Rico; 5 countries or territories in Asia (China, Hong Kong Special Administrative Region, Israel, Singapore, and Turkey); 18 countries in Europe; and Australia and New Zealand. Survival was in the range 50–59% in 5 countries or territories in Central and South America

(Argentina; Ecuador; Martinique, France; Peru; and Uruguay) and in 6 countries in Europe (Bulgaria, Latvia, Lithuania, Malta, Poland, and the Russian Federation), most of which have low or medium HDI. Between 2000 and 2014, 5-year survival increased by 4–6% in Japan and in 11 European countries and by 10% in India. In China, it increased from 53% for women diagnosed in 2000–2004 to 68% for those diagnosed in 2010–2014. Survival trends could not be systematically assessed in Africa, because the data were incomplete (Allemani et al., 2018).

1.1.6 Prevalence of HPV infection in women

Cervical cancer incidence often reflects exposure to HPV, which is the central cause of cervical cancer (see Sections 1.2.1 and 1.2.2). A meta-analysis evaluated more than 500 studies that tested for HPV infection in 2.4 million women aged 15 years and older with normal cytology (Bruni et al., 2016), including population-based studies, screening studies, and representative control series in case–control studies. The global pooled prevalence was 15.3% for any HPV infection, 70% of which were with carcinogenic types. The age-standardized overall prevalence of HPV infection by world region is presented in Fig. 1.7. The Caribbean has the highest prevalence (50.7%), and Southern Asia has the lowest (8.5%). [Some estimates may be unstable for regions with few studies or with studies in subpopulations.] The age-specific analysis (Fig. 1.8) shows that the prevalence of HPV infection is highest in younger women and lower in older women, and that the pattern appears flatter for Asia than for other regions. For some regions, such as Northern and Western Africa and Central America, there is a modest second peak of HPV prevalence in women older than 40 years. In studies with specific information on HPV type distribution, HPV16 was the most common type in all regions (standardized prevalence, 3.5%); HPV18 (1.3%), HPV52 (1.3%), HPV58 (1.0%), and HPV31 (0.9%)

Fig. 1.7 Standardized prevalence of human papillomavirus (HPV) infection by world region
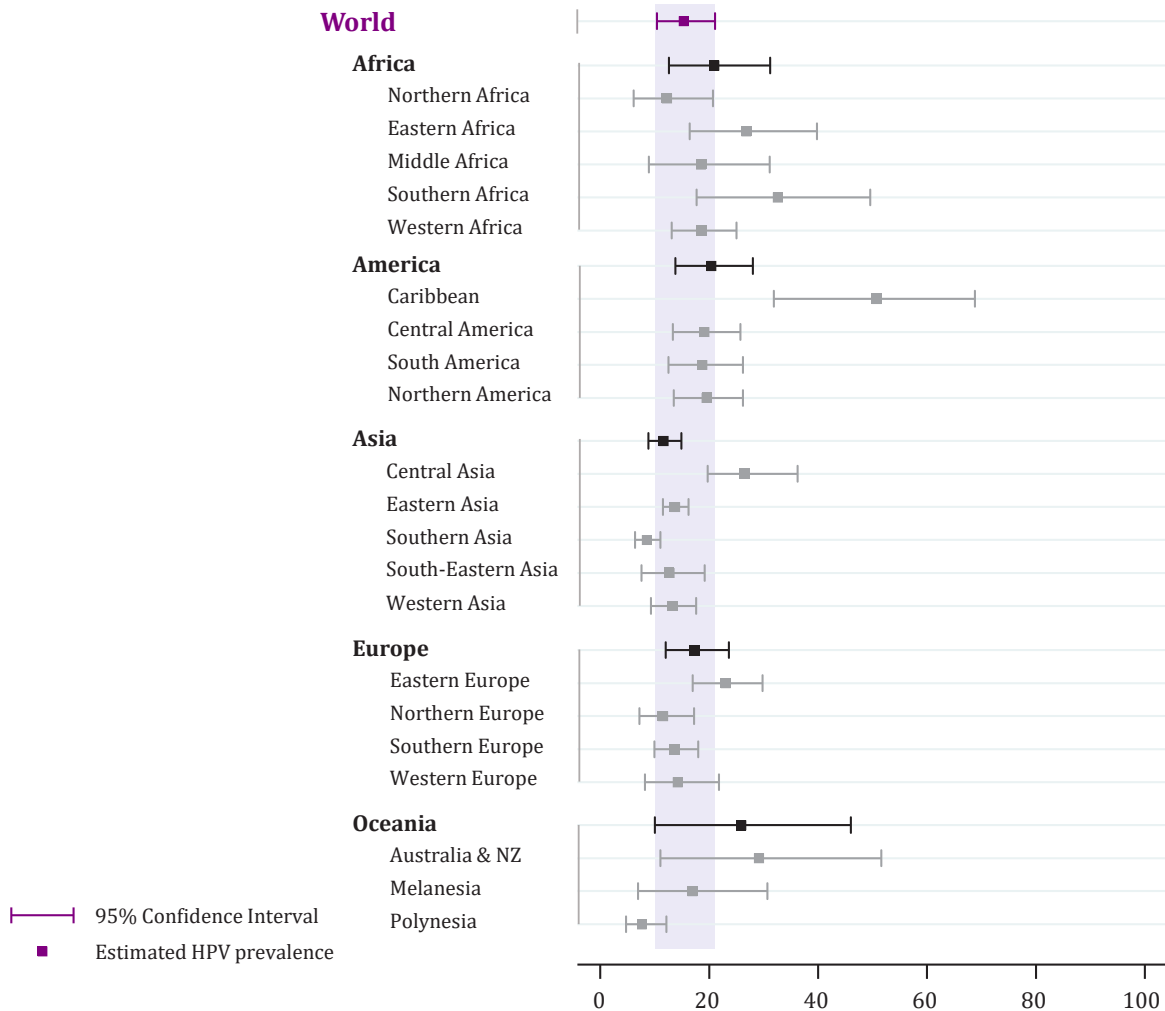
Squares represent the estimated adjusted HPV prevalence from the random-effects models for each corresponding region.
Courtesy of Laia Bruni, Bruni et al. (2016).

were the other most common carcinogenic HPV types (Bruni et al., 2016).

Most HPV prevalence surveys have been conducted in women, and very few population-based data exist for men.

1.1.7 Projections of global burden

Table 1.1 shows the estimated global burden of cervical cancer incidence and mortality in 2020 and projected to 2040, overall and by HDI category. Overall, a 32.0% increase in the estimated

number of new cases and a 40.8% increase in the number of deaths are projected by 2040. Numbers of deaths are projected to increase more rapidly in countries with lower HDI, and relatively large increases are projected in countries with medium and high HDI. These projections take into account only global demographic changes in population structure and growth according to United Nations estimates. The risk of developing or dying from cervical cancer is assumed to remain constant, and no allowance

Fig. 1.8 Age-specific standardized prevalence of human papillomavirus (HPV) infection by world region
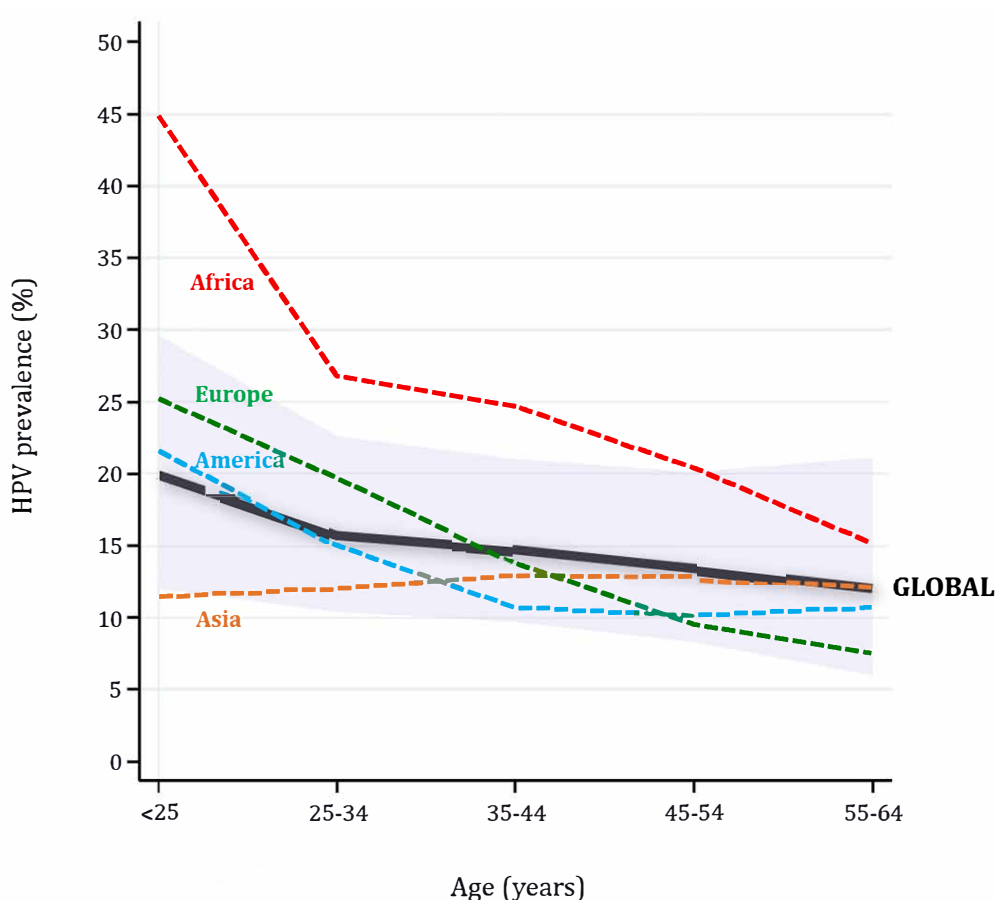
The shaded area represents the 95% confidence interval for the global HPV prevalence.
Courtesy of Laia Bruni, Bruni et al. (2016).

is made for changes in increased detection or improvements in survival. Modelling studies have also projected that the number of new cases per year will increase from 600 000 in 2020 to 1.3 million in 2069; these projections also take into account changes in underlying demographics and exposure to risk factors (Simms et al., 2019). Widespread coverage of both HPV vaccination and screening has the potential to decrease the incidence of cervical cancer in the future (Brisson et al., 2020).

1.2 Cervical neoplasia

1.2.1 Biology of HPV and of the cervix relevant to carcinogenesis and screening

HPVs are a group of circular, double-stranded DNA viruses of about 8000 base pairs that infect human skin and mucosal epithelia. The group includes more than 200 different genotypes, which are numbered in order of discovery and characterization. The small genomes of the HPV types that cause cervical cancer consist of an upstream regulatory region and six early (E)

Table 1.1 Global burden of cervical cancer: estimated annual numbers of incident cases and deaths, by HDI category and overall, in 2020 and projected to 2040

HDI category[a]	Population in 2020		Number of new cases (thousands)		Increase	Number of deaths (thousands)		Increase
	(millions)	(%)	2020	2040	(%)	2020	2040	(%)
Low HDI	494	12.8	82	162	97.3	56	112	99.9
Medium HDI	1136	29.4	183	292	59.6	113	189	66.8
High HDI	1442	37.3	240	297	23.5	129	182	40.6
Very high HDI	791	20.5	99	105	6.1	43	51	18.0
World	3863	100	604	798	32.0	342	481	40.8

HDI, Human Development Index.

[a] The four tiers of HDI are: low (< 0.55), medium (≥ 0.55 to < 0.7), high (≥ 0.7 to < 0.8), and very high (≥ 0.8).

Created using data from Ferlay et al. (2020) and UNDP (2020). Courtesy of Jérôme Vignat.

and two late (L) genes on the positive coding strand. The early genes are involved in viral replication and maintenance within the host cell; L1 and L2 encode the self-assembling major and minor capsid proteins, respectively (Schiffman et al., 2016).

Evolutionary taxonomy predicts the cells that specific HPV types infect and their carcinogenicity (Schiffman et al., 2005). The stable HPV genome has evolved very slowly in parallel with human evolution. The alpha genus contains 14 species, including more than 50 mucocutaneous types (Bzhalava et al., 2015); a single evolutionary branch includes the four species that contain the dozen or so HPV types that cause almost all cervical cancers (Fig. 1.9). The 12 types classified by IARC as carcinogenic to humans (Group 1) are HPV16, HPV31, HPV33, HPV35, HPV52, and HPV58 in alpha-9; HPV18, HPV39, HPV45, and HPV59 in alpha-7; HPV51 in alpha-5; and HPV56 in alpha-6 (Bouvard et al., 2009). In addition, HPV68 in alpha-7 is classified as probably carcinogenic to humans (Group 2A). The IARC classification refers to the carcinogenic potential based on prevalence in cervical cancers, not potency. Rarely, cervical cancers are found that contain only HPV types that are classified as possibly carcinogenic to humans (Group 2B), such as HPV73, but the attributable fraction and

absolute risk are very low (Schiffman et al., 2009; de Sanjose et al., 2010) (Fig. 1.10).

There is great variation in cervical carcinogenicity between the 12 HPV types that are classified by IARC in Group 1, and the importance of specific carcinogenic types may differ, depending upon the specific geographical population (Guan et al., 2012; de Martel et al., 2017; de Sanjosé et al., 2018; Demarco et al., 2020). The etiological fractions of the types can best be determined by analysing cervical cancer case series, which now include tens of thousands of cases of (mainly squamous) invasive cancer (Fig. 1.10) (Combes et al., 2015). Five categories can be distinguished on the basis of cancer risk: HPV16 (in the alpha-9 species) is singularly carcinogenic and causes about 60% of cases of SCC. HPV18 and HPV45 (in the alpha-7 species) cause 15% and 5% of SCC cases, respectively. Other closely related alpha-9 types (HPV31, HPV33, HPV35, HPV52, and HPV58) together account, with some regional variation, for 15% of SCC cases. The remaining carcinogenic types (HPV39 and HPV59 in alpha-7, HPV51 in alpha-5, and HPV56 in alpha-6) are much less carcinogenic and together cause about 5% of SCC cases. HPV-associated cases of adenocarcinoma, which are an uncommon histological group globally, are caused half by variants

Fig. 1.9 Phylogeny of the alpha human papillomavirus (HPV) types, with species groups and IARC classifications of the branch that contains carcinogenic types
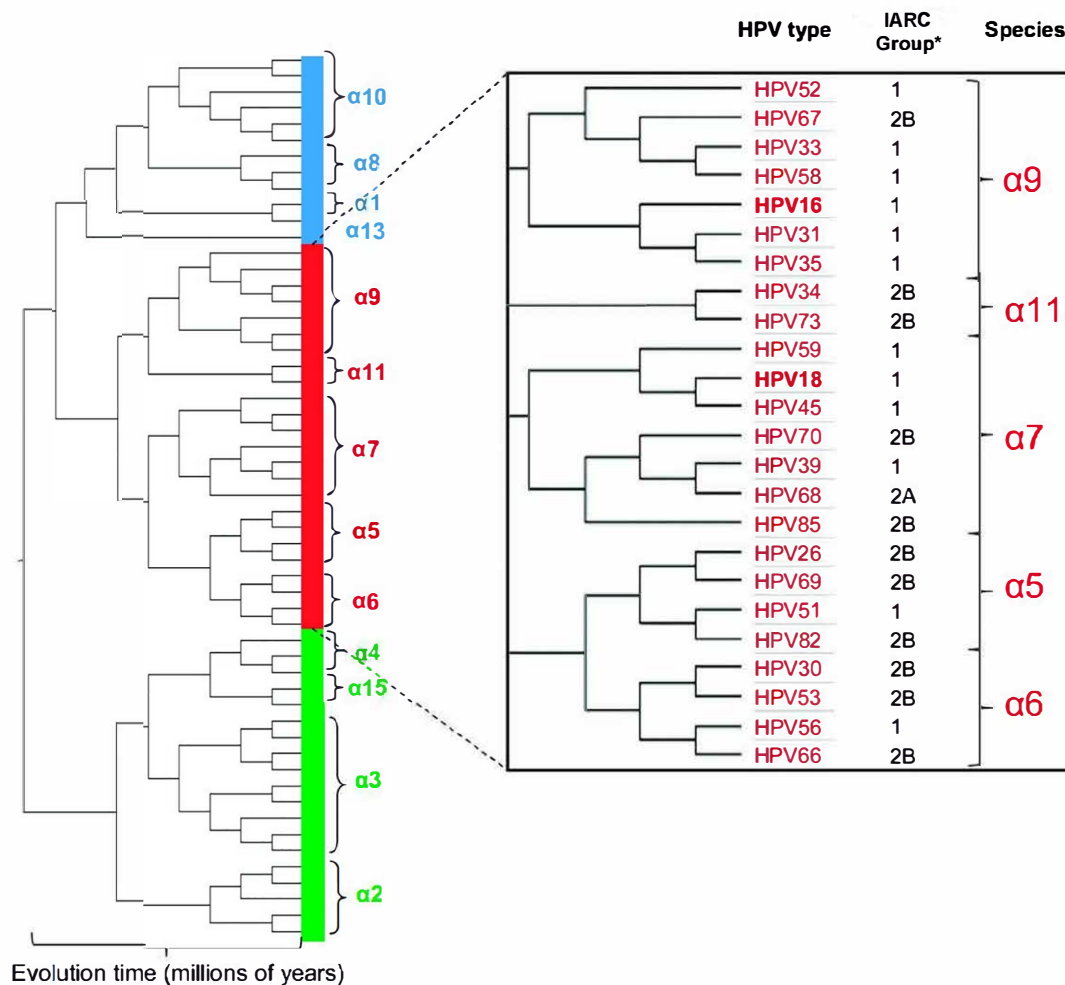
Note that almost all alpha-9 types (HPV16-associated) are carcinogenic. The other most important carcinogens are HPV18-associated, in alpha-7. There is no absolute division between carcinogenic and not carcinogenic; several of the types in this branch are classified as possibly carcinogenic to humans (Group 2B), because of genetic relatedness and because they have very rarely been associated with cancer cases.
* Carcinogenic to humans (Group 1); probably carcinogenic to humans (Group 2A); possibly carcinogenic to humans (Group 2B) (IARC, 2012). Reprinted from Schiffman et al. (2005). Copyright 2005, with permission from Elsevier.

of HPV16 and half by HPV18 or HPV45 (and only uncommonly by other types, particularly in alpha-7) (Guan et al., 2013).

This grouping is supported by a recent prospective study of large numbers of type-specific HPV infections and the absolute risk of cervical intraepithelial neoplasia grade 3 (CIN3) and adenocarcinoma in situ (AIS) (Demarco et al., 2020).

To optimize cervical screening using HPV testing requires knowledge of the relative importance of the carcinogenic HPV types in a specific region. For the purposes of screening and vaccination, each type can be considered as a single invariant virus. Nonetheless, for deeper understanding, epidemiological study, and possible future applications, each HPV type can be further divided phylogenetically into several

Fig. 1.10 Relative importance of the carcinogenic human papillomavirus (HPV) types

HPV type	HPV species	IARC Group[a]	% HPV type prevalence in cancer	% HPV type prevalence in normal	Odds ratio	% Attributable (etiological) fraction
HPV16	**α-9**	**Group 1**	**55.8**	**2.6**	**47.6**	**62.4**
HPV18	**α-7**	**Group 1**	**14.3**	**1**	**15.7**	**15.3**
HPV45	**α-7**	**Group 1**	**4.8**	**0.6**	**8.3**	**4.8**
HPV33	**α-9**	**Group 1**	**4**	**0.6**	**7.1**	**3.9**
HPV58	**α-9**	**Group 1**	**4**	**0.8**	**5.1**	**3.7**
HPV31	**α-9**	**Group 1**	**3.5**	**1**	**3.7**	**2.9**
HPV52	**α-9**	**Group 1**	**3.2**	**1**	**3.3**	**2.6**
HPV35	**α-9**	**Group 1**	**1.6**	**0.4**	**3.9**	**1.4**
HPV59	**α-7**	**Group 1**	**1.2**	**0.4**	**2.9**	**0.9**
HPV39	**α-7**	**Group 1**	**1.3**	**0.6**	**2.0**	**0.8**
HPV68	**α-7**	**Group 2A**	**0.6**	**0.4**	**1.5**	**0.2**
HPV51	**α-5**	**Group 1**	**1**	**0.9**	**1.2**	**0.2**
HPV56	**α-6**	**Group 1**	**0.8**	**0.6**	**1.3**	**0.2**
HPV73	α-11	Group 2B	0.5	0.3	1.8	0.2
HPV26	α-5	Group 2B	0.2	0.1	4.1	0.2
HPV30	α-6	Group 2B	0.2	0.1	2.6	0.1
HPV69	α-5	Group 2B	0.2	0.1	1.4	0.1
HPV67	α-9	Group 2B	0.3	0.2	1.2	< 0.1
HPV82	α-5	Group 2B	0.2	0.1	1.2	< 0.1
HPV34	α-11	Group 2B	0.1	0.1	1.0	Not attributable
HPV66	**α-6**	**Group 2B**	**0.3**	**0.6**	**0.4**	**Not attributable**
HPV70	α-7	Group 2B	0.2	0.8	0.3	Not attributable
HPV53	α-6	Group 2B	0.5	1.1	0.4	Not attributable

There is substantial variability in carcinogenicity between HPV types, including those classified by IARC in Group 1. However, for clinical use, commercial HPV screening assays often detect a pool of carcinogenic (or high-risk) HPV types; the 14 types most commonly included in current HPV tests are shown in bold here.

The attributable fraction is the percentage of cancer caused by that type. For each type, a relative risk can be estimated by the odds ratio of positivity in invasive cervical cancer compared with cytologically normal controls. A worldwide pooled analysis of invasive cancers (n = 13 763–40 706 cases, depending on type) and normal controls (n = 26 599–263 971, depending on type) reveals a five-level natural grouping in attributable fraction, shown by colour bands. (Attributable fractions are weighted to sum to 100%.) HPV16 is uniquely carcinogenic (red). HPV18 and HPV45 are relatively important for cancers (orange), especially adenocarcinomas, rather than precancers. Then follow other alpha-9 types related to HPV16 (yellow) and a group of less carcinogenic types (dark green), all classified by IARC in Group 1 or Group 2A. Last, there are types classified by IARC in Group 2B (light green), some of which contribute very small attributable fractions and some of which cannot be attributed at all. [For HPV66, which is more prevalent in normal cytology than in invasive cervical cancer and is sometimes mistakenly included in HPV screening tests, the attributable fraction is zero.]

[a] Carcinogenic to humans (Group 1); probably carcinogenic to humans (Group 2A); possibly carcinogenic to humans (Group 2B) (IARC, 2012).
Created by the Working Group using data from Combes et al. (2015). Courtesy of Gary Clifford.

variants and subvariants, which in turn consist of many subtly varying genomes (Burk et al., 2013; Chen et al., 2018). These individual genome differences inform our understanding of evolution (García-Vallvé et al., 2005; Van Doorslaer & Burk, 2010), fine differences in carcinogenicity (Cullen et al., 2015), and racial differences in response to specific HPV types (e.g. the prevalence of particular variants of HPV35 explains the higher percentage of cancers in women of African ancestry) (Pinheiro et al., 2020).

Fig. 1.11 Topology of human papillomavirus (HPV) infection of the cervix
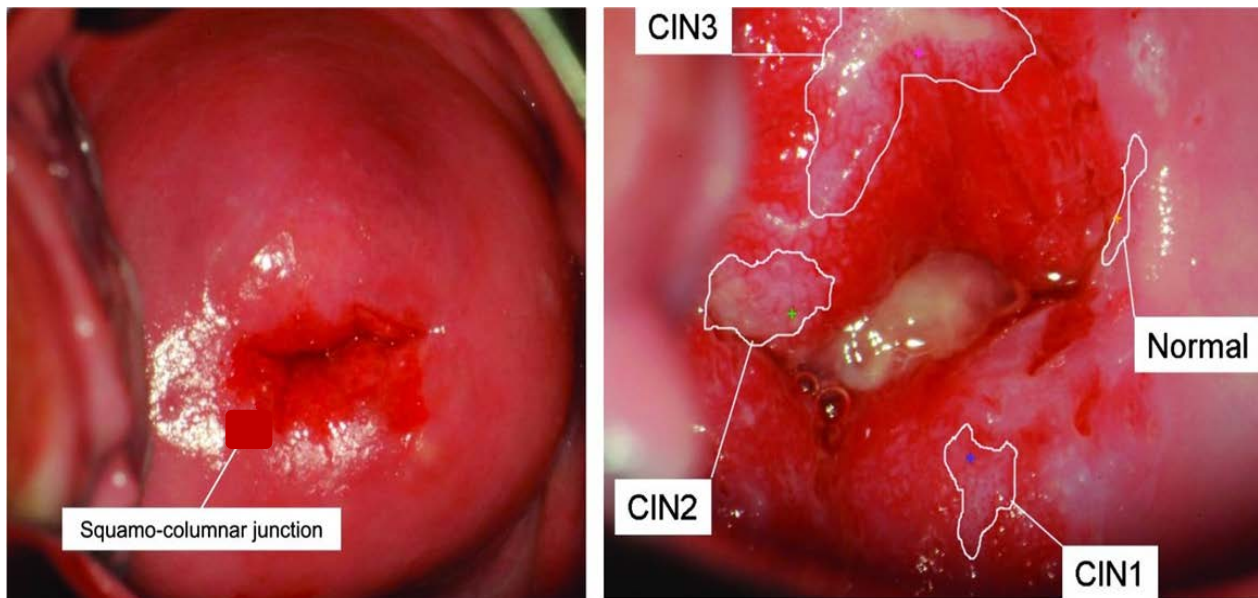
Most cervical cancers arise in a zone of uniquely susceptible tissue at the dynamic squamocolumnar junction. Multiple concurrent and asynchronous infections can cause clonal lesions of varying severity, which are difficult to distinguish visually. The cervical intraepithelial neoplasia (CIN) scale is found to be difficult to replicate either visually or microscopically. The available evidence suggests that a more reliable distinction can be made between signs of HPV infection and high-grade precursor lesions (precancer).
From Schiffman et al. (2011).

Another area of biology that affects screening strategies is the adequate definition of the cervix from a screening perspective. Anatomically, the cervix is defined as the terminal part of the uterus extending into the anterior aspect of the vagina, and it is composed of fibrous connective tissue, scant smooth muscle, and overlying epithelial components. However, from the perspective of carcinogenesis and screening, the cervix can be viewed as a ring of epithelium positioned at the junction between the glandular endocervix and the adjoining squamous ectocervix (Doorbar & Griffin, 2019). Multiple HPV infections and related clonal lesions of differing severity can be observed concurrently by cervical micro-dissection studies (Fig. 1.11) (Quint et al., 2001; Wentzensen et al., 2009; van der Marel et al., 2014; Venetianer et al., 2020). Cervical lesions can collide and seemingly merge, but each clone contains a single driving HPV infection.

Cervical cancers typically arise adjacent to the squamocolumnar junction (SCJ), which is subject to lifelong squamous metaplasia, the inward-moving gradual replacement of single-cell-thick columnar or glandular epithelium by the thicker squamous epithelium. Thus, the position of the SCJ moves centrally throughout a woman's life, from its distal origin on the ecto-cervix or vagina into the endocervical canal, until it has gradually moved out of the visible area in most older women. The ring of tissue between the early and eventual late SCJ positions, called the transformation zone (TZ), contains a compartment of immortal cells, which have an elevated risk of HPV-induced cervical cancer compared with the flanking tissues of the vagina or the deeper endocervix (Doorbar & Griffin,

2019). Cell sample collection and destruction of the TZ are the basis of secondary prevention of cervical cancer (see Section 1.2.5). Depending on the position of the SCJ, the cells collected during cervical screening will be mainly glandular cells, a mixture of TZ cell types, or mature squamous cells (Castle et al., 2006).

1.2.2 Transmission and natural history of HPV infection and multistage cervical carcinogenesis

Each individual case of cervical cancer arises from persistent infection with a specific carcinogenic HPV genome (Schiffman et al., 2016). Although it is well researched, cervical carcinogenesis has an unpredictable quality, because a woman may successfully control a large number of concurrent or asynchronous HPV infections but fail, for reasons that are still unexplained, to control the causal one. The whole process typically takes decades from acquisition of HPV infection to cancer diagnosis, although more rapid transitions are sometimes seen.

There is a well-established set of necessary health states and transitions leading from the normal cervix to invasive cancer (Fig. 1.12) (Campos et al., 2021). The schema presents the necessary transition states that are currently measurable with reasonable international reproducibility by a combination of HPV typing and expert gynaecological pathology: normal cervix (uninfected), HPV infection (type-specific carcinogenic), precancer, and cancer. The transition between normal cervix and HPV infection can be called appearance and disappearance of HPV detection, to acknowledge the limitations of existing measurement assays and the potential for reactivation of latent infections. The transitions between infection and precancer are described as progression to and regression of precancer. Invasion is considered a typically irreversible transition when HPV-associated cells cross the basement membrane. Precancers

and cancers are subdivided into the predominant squamous pathway and the uncommon glandular pathway, not only because the histological types vary clinically but also because the observed transition probabilities from infection to precancer to cancer seem to differ (Schiffman et al., 2016). Fig. 1.13 shows the parallel between HPV infection and cervical carcinogenesis at the levels of molecular pathogenesis and clinical microscopic or visual diagnoses.

As shown in Fig. 1.12, the cervix uninfected by carcinogenic HPV is considered normal from the point of view of cervical cancer risk, i.e. at extraordinarily low risk of prevalent or near-term incident cancer. Vertical transmission is not known to be an important factor in cervical carcinogenesis (Zahreddine et al., 2020). Anogenital HPV infections are very readily transmitted through direct physical, i.e. sexual (not necessarily intromissive), contact (Malagón et al., 2019). The average age at the start of sexual activity in a population determines the average starting time point of cervical carcinogenesis (Kjaer et al., 1992).

For any given infection, the moment of acquisition is not precisely known. Detection (i.e. appearance) of HPV can represent primary acquisition or reappearance after one or more episodes of disappearance (the two are, in practical terms, indistinguishable) (González et al., 2010). The closer a woman is in age to the start of her sexual activity, the more likely it is that appearance represents a truly new acquisition (Ho et al., 1998; Maucort-Boulch et al., 2010).

Following the general epidemiological principle, the prevalence odds of HPV infection = incidence × duration (i.e. persistence); when prevalence is low, the equation reduces to prevalence = incidence × duration. In women without evidence of prevalent precancer, the HPV types most commonly found on screening (i.e. prevalent infections) are also the most likely to appear during follow-up (i.e. incident infections). The strong correlation between HPV

Fig. 1.12 Human papillomavirus (HPV) infection and multistage development of cervical cancer
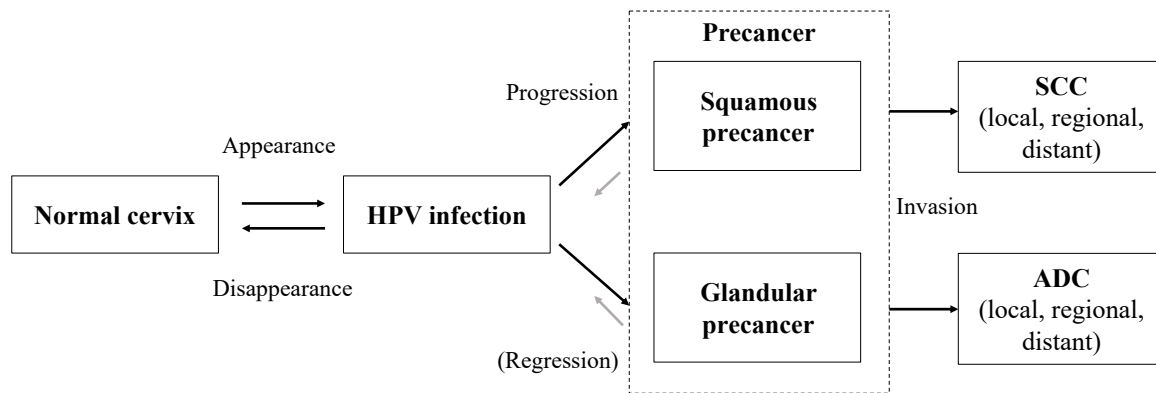
Each box in the figure represents a necessary stage, or health state, on the path to cervical cancer. The arrows represent forward and backward transitions between health states. The transitional probabilities form a basis of epidemiological research and health decision models.
ADC, adenocarcinoma; SCC, squamous cell carcinoma.
Reproduced with permission from Campos et al. (2021).

appearance and prevalence, which is seen in all age groups, holds because the pattern of disappearance (often called clearance) is nearly the same for all HPV types (including non-carcinogenic types) in immunocompetent women, irrespective of age (Plummer et al., 2007; Demarco et al., 2020). The clearance curve is very distinct, with extremely rapid disappearance of a high proportion of infections in the initial months, leading to median clearance by about 1 year in most screen-detected infections, with a large fraction undetectable within 2–3 years. Only a very small proportion of carcinogenic HPV infections are detectable for more than 5 years (without progression to precancer) (Ho et al. 1998; Demarco et al., 2020).

The disappearance of HPV can indicate immune control (resulting in latent infections, which replicate in the basal epithelial layer without a complete life-cycle and full virion production) or complete eradication from the cervix (Doorbar, 2018). The distinction cannot currently be measured; in any case, only persistently apparent infections, detectable for years by HPV DNA assays, confer risk of precancer.

Progression to precancer is a function of HPV type and time of persistence (Fig. 1.14) (Schiffman et al., 2005; Rodríguez et al., 2010). Compared with these major influences, progression is increased only slightly by etiological cofactors such as smoking, multiparity, or use of hormonal contraceptives (Perkins et al., 2020). Whereas viral clearance follows a curve that is initially very fast and then slows, progression is a more linear product of time spent as persistently detectable. HPV16 has the highest progression rate per time (Demarco et al., 2020). The lowest-risk carcinogenic types have considerably lower progression rates.

The prevalence of HPV in adult women in a population is a critical determinant of cervical screening and triage strategies, because most infections are acquired in young adulthood and resolve; prevalently detected HPV infections in mid-adult and older women are more likely to be persistent infections that have not resolved. In screening, point prevalent infections are observed; if prevalence is high, it becomes impractical to treat all infected women by use of currently available destructive or excisional

Fig. 1.13 Major steps in the development of cervical cancer
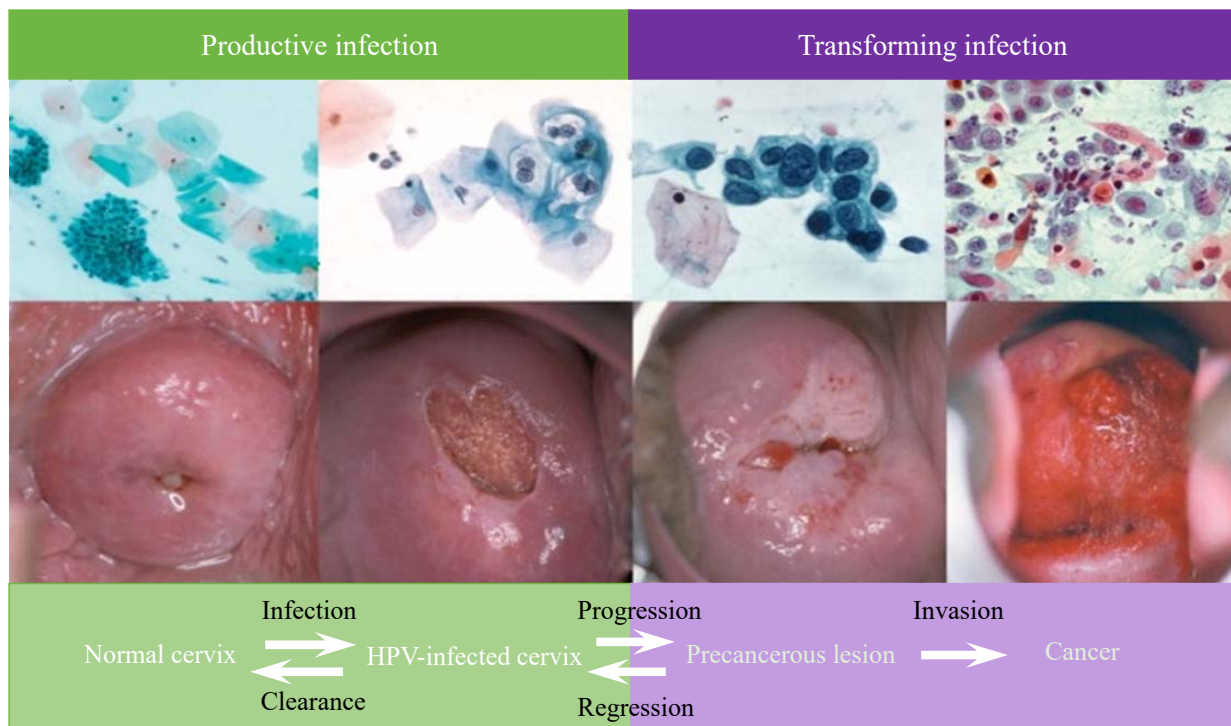
Reprinted from Schiffman et al. (2007). Copyright 2007, with permission from Elsevier. Adapted from Schiffman & Castle (2005).

methods. International studies of prevalence of carcinogenic HPV types indicate that low prevalence in mid-adulthood is characteristic of immunocompetent, frequently screened populations (Fig. 1.15) (Bruni et al., 2010). However, a high prevalence throughout adulthood is observed in some important regions, such as sub-Saharan Africa, and may be linked to partial immunodeficiency (or, alternatively, to some unknown behavioural difference combined with lack of screening). The partial immuno-deficiency hypothesis suggests that there is a tolerant immune response secondary to chronic parasitoses or gut helminth prevalence (Petry et al., 2003; Gravitt et al., 2016). Women living with HIV are an important special population; they have a high HPV prevalence, and screening

and management require separate consideration (see Section 5.2.1).

Few studies of type-specific regression of precancer have been conducted, because of the ethical requirement for prompt treatment. However, it is well established that HPV type is a key determinant of the precancerous state and the risk of progression. The carcinogenic and non-carcinogenic HPV types found in precancers, even when stringently defined as CIN3 or AIS, are more numerous (specifically for CIN3) than the types found in invasive cancer (Guan et al., 2012) (Fig. 1.10). This shows that current clinical definitions of precancer are not perfect surrogates of cancer risk. HPV31 and HPV51 are examples of HPV types whose role in causing precancers may lead to an exaggerated view of their importance for cancers. Similarly, HPV53

Fig. 1.14 Average clearance, persistence, and progression of carcinogenic human papillomavirus (HPV) infections
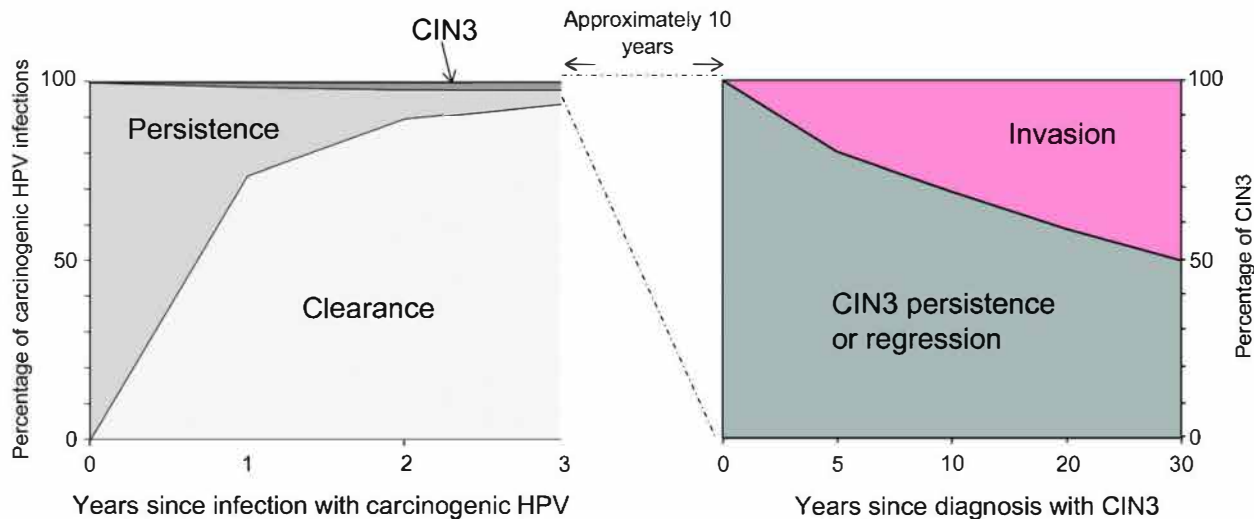

This figure combines the early natural history of rapid clearance of HPV infection with slower progression to precancers, which can, in turn, eventually invade, as described by McCredie et al. (2008).
CIN3, cervical intraepithelial neoplasia grade 3.
Reproduced from Schiffman et al. (2011).

and HPV66, two types that are possibly carcinogenic to humans (Group 2B), are frequent causes of precancer but almost never cause cancer (Schiffman & de Sanjose, 2019). Type-specific transition probabilities of invasion cannot be directly observed ethically (McCredie et al., 2008); however, they can be crudely ranked by the relative proportions of the individual types in cancers versus precancers in a given population (Guan et al., 2012) (Fig. 1.10). A higher relative proportion in cancers suggests an association with invasive potential, as exemplified by the predominance of HPV16 in invasive cancers.

The epidemiology of HPV natural history and multistage cervical carcinogenesis can also be viewed in molecular terms describing type-specific viral carcinogenicity. Viral genomes persist at low levels in the undifferentiated cells in the lowest layers of the epithelium, typically with only low (and regulated) levels of viral gene expression. This is the reservoir of infection that underlies viral latent persistence. As cells from this layer differentiate and migrate towards the epithelial surface, a pattern of gene expression is initiated, which leads to the production of virus particles; these are eventually shed from the epithelial surface (Doorbar, 2018). The cellular immune system, a combination of intraepithelial and stromal cellular surveillance and destruction of infected cell clones, plays an important role in controlling HPV infections in cervical tissue (Stanley et al., 1994). Sometimes, if cellular immune control weakens (e.g. due to immune senescence), infections persisting in a latent, non-infectious state may be reactivated and resume a full viral life-cycle, leading to virion production and release (Schiffman et al., 2016). The risk of subsequent precancer after reappearance is equal to or lower than the risk after first acquisition (Rodríguez et al., 2012; Gage et al., 2014).

Fig. 1.15 Factors that influence age-specific human papillomavirus (HPV) prevalence in women, and three patterns of HPV prevalence
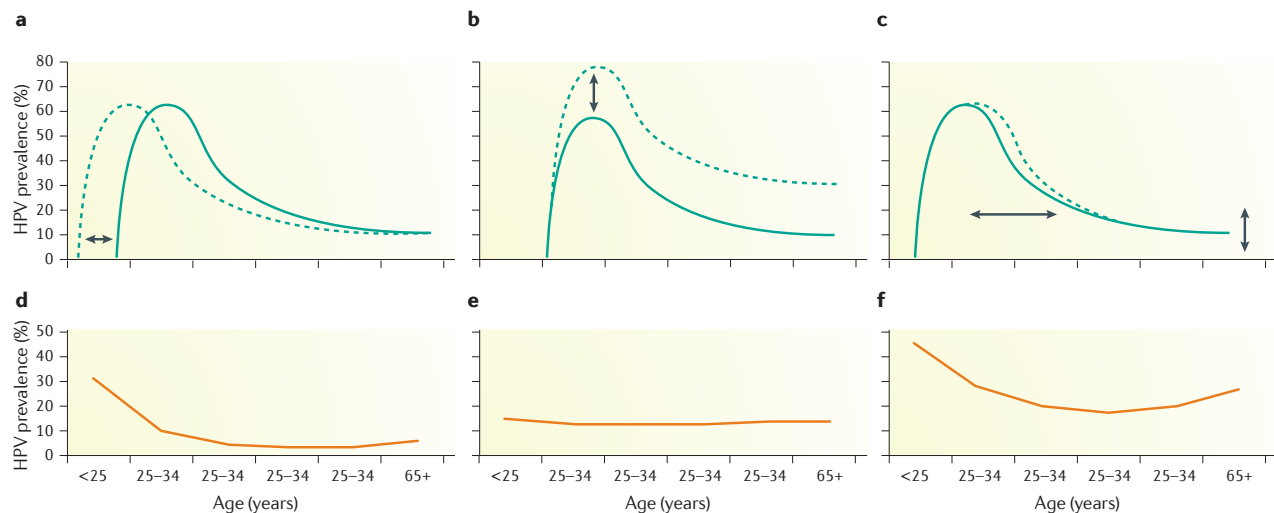
The prevalence of HPV and associated cellular and visual changes in mid-adulthood is a critical determinant of screening and management strategies. Prevalence patterns by age vary widely between settings, because of behavioural and immunological variables. Examples are given in (a), (b), and (c). (a) Age at first sexual intercourse determines the beginning of the curve. (b) Sequential and concurrent multiple sexual partnership (both sexes) determines the height. (c) Partner stability and/or immune response shape the curve descent, and cervical cancer screening practices determine the height at older ages. Three illustrative examples of age-specific HPV prevalence are given in (d), (e), and (f): (d) more-developed regions, (e) India, and (f) Africa.
Adapted from Schiffman et al. (2016).

The difference between productive HPV infection and precancer has been studied comprehensively at the molecular level, and there are important changes in both viral and cellular biology. HPV infections are very common, and even infections with carcinogenic types are usually benign. However, when they are persistent, infections with carcinogenic types may shift from the usual and common productive state (i.e. the complete life-cycle designed to produce new virus particles). Instead, the virus can enter an abortive or transforming state characteristic of precancer. This occurs when the viral proteins used for cellular adaptation in the successful vegetative life-cycle disrupt cell differentiation and, as an unintended consequence, are no longer able to generate infectious virus. The correlated visual, microscopic, and molecular signs or biomarkers of the shift from productive

infection to transforming infection underlie almost all cervical screening, triage, and diagnostic tests designed to detect precancer.

At the molecular level, viral gene expression changes from a productive infection characterized by expression of the E4, L2, and L1 viral genes to a strongly increased expression of the viral oncogenes E6 and E7 (Doorbar et al., 2012; Griffin et al., 2015). This deregulated expression of E6 and E7 in replicating basal cells leads to disturbances of cell-cycle regulation, disrupted differentiation and cell density regulation, and abrogation of apoptosis. The changes include disruption of the retinoblastoma protein (pRB) family regulatory pathway by E7, which results in accumulation of p16; detection by p16/Ki-67 dual staining provides accurate cytological and histological markers of precancer (Wentzensen et al., 2007, 2019). Deregulated expression of E6

Table 1.2 Summary of the current WHO classification of tumours of the uterine cervix

Squamous cell tumours and precursors	*Germ cell tumours*
Squamous intraepithelial lesions	*Neuroendocrine neoplasia*
Squamous cell carcinoma, HPV-associated	Neuroendocrine tumour
Squamous cell carcinoma, HPV-independent	Neuroendocrine carcinoma
Squamous cell carcinoma NOS	Small cell neuroendocrine carcinoma
Glandular tumours and precursors	Large cell neuroendocrine carcinoma
Adenocarcinoma in situ, HPV-associated	Mixed neuroendocrine–non-neuroendocrine neoplasms
Adenocarcinoma, HPV-associated	Carcinoma admixed with neuroendocrine carcinoma
Adenocarcinoma in situ, HPV-independent	*Mesenchymal tumours of the lower genital tract*
Adenocarcinoma, HPV-independent, gastric type	Adipocytic tumours
Adenocarcinoma, HPV-independent, clear cell type	Fibroblastic and myofibroblastic tumours
Adenocarcinoma, HPV-independent, mesonephric type	Vascular tumours
Other adenocarcinomas of the uterine cervix	Smooth muscle tumours
Other epithelial tumours	Skeletal muscle tumours
Carcinosarcoma	Peripheral nerve sheath tumours
Adenosquamous and mucoepidermoid carcinomas	Tumours of uncertain differentiation
Adenoid basal carcinoma	Undifferentiated small round cell sarcomas
Carcinoma, unclassifiable	*Melanocytic lesions*
Mixed epithelial and mesenchymal tumours	Naevi
Adenomyoma	Melanoma
Adenosarcoma	*Metastasis*

HPV, human papillomavirus; NOS, not otherwise specified.
Adapted from WHO Classification of Tumours Editorial Board (2020).

and E7 oncoproteins also affects DNA methylation; in transformed cells, HPV genomes are highly methylated throughout CpG sites, especially in the capsid encoding the L1 and L2 genes (yielding a biomarker predictive of precancer) (Lorincz et al., 2013; von Knebel Doeberitz & Prigge, 2019; see also Section 4.6).

1.2.3 Terminology for pathological classification

This section provides an overview of the classification and pathology of cervical cancer. The current WHO classification is summarized in Table 1.2, and the text below focuses on the most common cervical cancer types: SCC and adenocarcinoma, which typically arise in the TZ. These two tumour types account for more than 95% of all cervical cancers. SCC is considerably more common than adenocarcinoma, which

accounts for about 5% of all cervical carcinomas in non-screened populations, although more recently a higher proportion (10–25%) has been reported in screened populations (Smith et al., 2000; Adegoke et al., 2012). Other tumour types are rare, but screening programmes do identify appreciable numbers of them (Lei et al., 2019). The WHO classification of tumours of female genital tumours provides detailed information on all of the tumours and tumour-like lesions that arise in the uterine cervix (WHO Classification of Tumours Editorial Board, 2020).

Most cervical cancers are HPV-associated carcinomas, but a small percentage of tumours are not associated with HPV infection. Moreover, there is accumulating evidence that HPV-independent cervical carcinomas are more aggressive than their HPV-associated counterparts (Nicolás et al., 2019; Stolnicu et al., 2019). To reflect this, the classification of cervical

carcinomas has changed in the latest edition of the WHO classification, to separate tumours associated with HPV infection from those that arise independently of HPV (WHO Classification of Tumours Editorial Board, 2020).

(a) Etiology and pathogenesis

The etiology and pathogenesis of epithelial tumours of the cervix are dominated by HPV infection, as discussed in detail in Sections 1.2.1 and 1.2.2.

An important consequence of our improved understanding of the relationship between HPV infection and cervical cancer is that it has enabled reconsideration of the terminology of precursor lesions. HPV infections occur in two forms: productive and transforming. Productive HPV infection cannot occur in glandular epithelium, because it is tightly linked to squamous differentiation. However, transforming infection can occur in glandular epithelium, and this leads to the development of HPV-associated AIS, the precursor of HPV-associated adenocarcinoma. This has led to increasing use of a two-tier classification for HPV-associated squamous precursor lesions (Table 1.2).

(b) Epithelial tumours

(i) Precursors of squamous cell carcinoma

The histopathological classification of precursors of cervical SCC has changed over time (Fig. 1.16). Until the 1960s, non-invasive lesions were subdivided into carcinoma in situ and dysplasias, which were in turn subdivided into three grades (mild, moderate, and severe) of increasing cytological abnormality (Reagan et al., 1953). In 1967, Richart proposed the term cervical intraepithelial neoplasia (CIN) to encompass the spectrum of changes encountered in intraepithelial lesions of squamous epithelium (Richart, 1967). CIN lesions are identified on the basis of full-thickness nuclear abnormality, with the grades (CIN1, CIN2, and CIN3) determined traditionally by the position in the epithelium, in thirds, at which cytoplasmic maturation occurs; these features correlate with increasing risk of progression to invasive disease (Ostör, 1993; Cantor et al., 2005). Initially, carcinoma in situ (CIS) was separated from CIN3, but reproducible separation was problematic, and CIS was subsequently incorporated into the CIN3 category. The CIN system has been used widely, both for the diagnosis of cervical disease and, since the 1980s, in screening programmes, particularly in Europe (Fox et al., 1999; Hirschowitz et al., 2012). The alternative two-tier system (Lower Anogenital Squamous Terminology [LAST]), which recognizes low-grade and high-grade squamous intraepithelial lesions (SILs), has its origins in the Bethesda system for reporting cytopathology, in the late 1980s (Solomon, 1989), and has been translated into histopathological use, particularly in North America (Tabbara et al., 1992; Stoler et al., 2001). Broadly, low-grade SIL corresponds to a combination of the categories of CIN1 and HPV-associated changes without CIN; and high-grade SIL corresponds to a combination of CIN2 and CIN3. A detailed review of classification systems, together with considerations of HPV biology, led to the recommendation in 2012 that the SIL terminology be used (Darragh et al., 2012); this was endorsed in 2014 in the WHO classification (Kurman et al., 2014) and has been retained in the 2020 classification (WHO Classification of Tumours Editorial Board, 2020). Both LAST and WHO recommend that the appropriate CIN term is provided in parentheses after the SIL designation, for example "high-grade SIL (CIN2)". In cases where there is diagnostic uncertainty, p16 immunostaining, when available, is helpful (Darragh et al., 2012; Castle et al., 2020).

For cytology, the Bethesda (SIL) system is widely used, but the Pap and WHO systems are also used in some areas. This variation is also true for histopathology; both the CIN and LAST (SIL) systems are used in different geographical

Fig. 1.16 Classification systems currently used for squamous lesions of the cervix

Histology		Cytology			Molecular
CIN	LAST	Pap	WHO	Bethesda	
Normal	Normal	I	Negative	NILM	Normal cervix
		II	Squamous atypia	ASC-US	
CIN1	LSIL	III	Mild	LSIL	HPV infection
		IIID			
CIN2	HSIL	IV	Moderate	HSIL	Precancer
CIN3			Severe		
Cancer	Cancer	V	Cancer	Cancer	Cancer

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LAST, Lower Anogenital Squamous Terminology; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion and malignancy; Pap, Papanicolaou; WHO, World Health Organization.
Adapted from Schiffman et al. (2016).

regions. The relationship between the systems currently in use is shown in Fig. 1.16. This discussion relates to HPV-associated squamous precursor lesions. There are no validated reports of HPV-independent squamous precursor lesions, which are therefore not included in the WHO classification (WHO Classification of Tumours Editorial Board, 2020).

(ii) Squamous cell carcinoma

SCC is the most common type of cervical cancer, constituting 80–90% of cases (de Sanjose et al., 2010). SCC can be defined as a malignant tumour comprising invasive epithelium exhibiting squamous differentiation. This tumour can show several different histological patterns, for example keratinizing, non-keratinizing, basaloid, or papillary. These patterns aid diagnosis but do not influence clinical management. Most cervical SCCs (an estimated 93–95%) are HPV-associated (de Sanjose et al., 2010; Rodríguez-Carunchio et al., 2015; Nicolás et al., 2019). The presence of HPV can be determined

by molecular testing, but p16 immunohistochemistry is an effective surrogate marker of HPV in most cases (Klaes et al., 2001, 2002; Darragh et al., 2012). Immunohistochemistry for p16 is available in many, but not all, diagnostic laboratories, and therefore the WHO classification allows for a diagnosis of SCC not otherwise specified (NOS), in settings where the distinction between HPV-associated and HPV-independent tumours cannot be made by either p16 immunostaining or HPV testing (WHO Classification of Tumours Editorial Board, 2020).

(iii) Precursors of adenocarcinoma

In contrast to SILs, both HPV-associated and HPV-independent precursor lesions are recognized for adenocarcinomas of the cervix. The HPV-associated lesions, termed AIS, constitute the majority of cases and can generally be identified by their typical morphological features and diffuse positivity for p16 (Kurman et al., 2014; Stolnicu et al., 2018, 2019). The HPV-independent lesions have been increasingly recognized in

recent years, particularly as precursor lesions for HPV-independent adenocarcinoma of gastric type, which have been referred to historically as lobular endocervical glandular hyperplasia (LEGH) and atypical LEGH (Kawauchi et al., 2008; McCluggage, 2016; Mikami, 2020). Mesonephric remnant hyperplasia may be a precursor lesion for HPV-independent adenocarcinoma of mesonephric type (McCluggage, 2016).

(iv) Adenocarcinoma

Adenocarcinomas are defined as malignant tumours comprising invasive epithelium exhibiting glandular differentiation. They are also separated into HPV-associated and HPV-independent tumours (Stolnicu et al., 2018). Most cervical adenocarcinomas (75–90%) are HPV-associated, and typical cases of usual-type adenocarcinoma can be identified on the basis of haematoxylin and eosin morphology. p16 immunostaining and/or high-risk HPV testing can be helpful in confirming the diagnosis (Stolnicu et al., 2018). HPV-independent adenocarcinomas are less common and include gastric-type adenocarcinomas (incorporating adenoma malignum) (Nishio et al., 2019; Mikami, 2020), clear cell carcinoma, and mesonephric carcinoma. Gastric-type adenocarcinomas comprise 10–15% of all cervical adenocarcinomas worldwide (Stolnicu et al., 2018; Hodgson et al., 2019) and 20–25% of cervical adenocarcinomas in Japan (Kojima et al., 2007; Kusanagi et al., 2010; Wada et al., 2017). There is accumulating evidence that HPV-independent cervical carcinomas, particularly gastric-type adenocarcinomas, behave more aggressively than their HPV-associated counterparts (Nicolás et al., 2019; Stolnicu et al., 2019).

[It is important to recognize that screening programmes traditionally are not as effective for the identification of adenocarcinomas or their precursors; however, HPV-associated AIS and adenocarcinomas are identified more effectively by HPV testing than by cytology.]

(v) Neuroendocrine tumours

Low-grade neuroendocrine tumours (carcinoid and atypical carcinoids) are very rare in the cervix. High-grade neuroendocrine carcinomas of small cell and large cell type occur much more frequently, are typically HPV-associated (small cell, 85%; large cell, 88%; Castle et al., 2018), and may be accompanied by an HPV-associated adenocarcinoma component. These tumours tend to present at an advanced stage and behave aggressively (Gibbs et al., 2019).

(vi) Other epithelial tumours

This category includes adenosquamous carcinoma, in which there is a mixture of both adenocarcinoma and SCC, and rare tumour types such as adenoid cystic carcinoma and adenoid basal carcinoma. True adenoid cystic carcinoma must be distinguished from an HPV-associated carcinoma with an adenoid cystic growth pattern. Carcinosarcomas occur as primary cervical tumours and are considered metaplastic carcinomas (WHO Classification of Tumours Editorial Board, 2020).

(c) Non-epithelial tumours

Malignant non-epithelial tumours are rare in the cervix. An important tumour in this category is embryonal rhabdomyosarcoma, which typically occurs in young children and may be associated with *DICER1* syndrome, where it is associated with other syndromic tumours such as cystic nephroma, pleuropulmonary blastoma, and thyroid tumours (WHO Classification of Tumours Editorial Board, 2020).

1.2.4 Stage at diagnosis and survival

Tumour staging assesses the extent of tumour spread, and for many tumours it is the most important determinant of clinical management, largely because it is strongly associated with patient outcome. Staging assesses spread within the organ of origin, spread to local structures,

and spread to lymph nodes and distant sites; this forms the basis of the tumour–node–metastasis (TNM) staging system, which assigns separate categories to the tumour (T), lymph nodes (N), and metastases to distant sites (M) ([Fig. 1.17](#)).

Gynaecological tumours are typically also staged using the International Federation of Gynecology and Obstetrics (FIGO) staging system, which, for cervical carcinomas, is traditionally based on the extent of local spread and is designed to be clinically (rather than pathologically or radiologically) assessable. Most of the recent literature is based on the 2009 FIGO classification, which separates clinically visible disease from microscopically detected disease and assesses spread on the basis of involvement of other pelvic structures ([Pecorelli et al., 2009](#); [Brierley et al., 2017](#)). In 2018, the FIGO staging system was modified to include lymph node metastasis, based on either radiological or pathological assessment ([Table 1.3](#)) ([Bhatla et al., 2018, 2019](#); [Anonymous, 2019](#)). Patients with tumours confined to the cervix but with lymph node metastasis are now considered to have stage III rather than stage I disease. A second significant change in the 2018 system was the removal of lesion width assessment from the microinvasive disease categories. Thus, stage IA and microscopic stage IB disease are defined solely on the basis of depth of invasion.

A comparison of the 2009 and 2018 FIGO staging systems in a study of 1282 patients at a centre in the USA demonstrated upward stage migration in more than 50% of patients, largely because of the inclusion of lymph node metastasis in the 2018 system. This resulted in improved stratification of outcome, but heterogeneity remained, particularly for patients with stage III disease. Overall, progression-free survival at 5 years by the 2009 FIGO system versus the 2018 FIGO system was: stage I, 80% versus 87% ($P = 0.02$); stage II, 59% versus 71% ($P = 0.002$); stage III, 35% versus 55% ($P < 0.001$); and stage IV, 20% versus 16% ($P = 0.41$) ([Grigsby](#)

et al., 2020](#)). The differences for stages I, II, and III were statistically significant.

Improved discrimination of survival groups was also shown in a study focusing on stage IB and stage III disease using retrospective data from the Surveillance, Epidemiology, and End Results (SEER) Program ([Matsuo et al., 2019](#)). These are early data after these significant changes to the FIGO staging system, but there does appear to be improved patient stratification using the 2018 system.

Data from studies describing stage at diagnosis and stage-related survival are given in [Table 1.4](#), [Table 1.5](#), [Table 1.6](#), and [Table 1.7](#).

1.2.5 Treatment of cervical cancer and of precancerous lesions

The successful reduction of cervical cancer incidence or mortality requires appropriate follow-up and treatment of screen-positive women. Women with precancerous lesions are treated in order to prevent invasive cervical cancer. Treatment of precancer can be carried out by biopsies performed during colposcopy or as part of a screen-and-treat approach. Two main categories of treatment techniques are available: destructive and excisional. These aim to effectively eradicate precancerous lesions of the cervix, with minimal associated morbidity. For cervical cancer, treatment options rely mainly on radical surgery and radiotherapy. This section gives a short overview of the treatment options and refers mostly to the recent comprehensive IARC review ([Prendiville & Sankaranarayanan, 2017](#)) and WHO reports ([WHO, 2014](#), [2019](#), [2020](#)).

(a) Treatment of squamous precancerous lesions

Comprehensive colposcopic examination before the treatment enables the provider to determine the type and size of the TZ of the cervix and to recognize or rule out cancer, microinvasive disease, or precancer (see Section 4.5). The

Table 1.3 Staging of cervical carcinoma according to the 2018 FIGO staging system[a]

FIGO stage (2018)	Definition
I	The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion < 5 mm (all macroscopically visible lesions, even those with superficial invasion, are stage IB)
IA1	Measured stromal invasion < 3 mm in depth
IA2	Measured stromal invasion ≥ 3 mm and < 5 mm in depth
IB	Clinically visible lesion confined to the cervix or invasive carcinoma with measured deepest invasion ≥ 5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumour diameter[b]
IB1	Invasive carcinoma ≥ 5 mm depth of stromal invasion, and < 2 cm in greatest dimension
IB2	Invasive carcinoma ≥ 2 cm and < 4 cm in greatest dimension
IB3	Invasive carcinoma ≥ 4 cm in greatest dimension
II	The carcinoma invades beyond the uterus but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma < 4 cm in greatest dimension
IIA2	Invasive carcinoma ≥ 4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes (including micrometastases),[c] irrespective of tumour size and extent (with r and p notations)[d]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (bullous oedema alone does not indicate stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

FIGO, International Federation of Gynecology and Obstetrics.

[a] Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumour size and extent, in all stages. Pathological findings supersede imaging and clinical findings.

[b] The involvement of vascular or lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c] Isolated tumour cells do not change the stage, but their presence should be recorded.

[d] Add the notation r (imaging) or p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r, and if confirmed by pathological findings, it would be stage IIIC1p. The type of imaging modality or pathology technique should always be documented. When in doubt, the lower stage should be assigned. Compiled from Bhatla et al. (2018, 2019) and Anonymous (2019).

Fig. 1.17 Tumour−node−metastasis (TNM) staging of tumours of the cervix uteri

(ICD-O-3 C53)

The definitions of the T and M categories correspond to the FIGO stages. Both systems are included for comparison.

Rules for Classification

The classification applies only to carcinomas. There should be histological confirmation of the disease.

The following are the procedures for assessing T, N, and M categories:

T categories   Clinical examination and imaging*
N categories   Clinical examination and imaging
M categories   Clinical examination and imaging

Note
* The use of diagnostic imaging techniques to assess the size of the primary tumour is encouraged but is not mandatory. Other investigations, e.g., examination under anaesthesia, cystoscopy, sigmoidoscopy, intravenous pyelography, are optional and no longer mandatory.

The FIGO stages are based on clinical staging. For some Stage I subdivisions (IA–IB1) are mainly pathological, including the histological examination of the cervix. (TNM stages are based on clinical and/or pathological classification.)

Anatomical Subsites

1. Endocervix (C53.0)
2. Exocervix (C53.1)

Regional Lymph Nodes

The regional lymph nodes are the paracervical, parametrial, hypogastric (internal iliac, obturator), common and external iliac, presacral, lateral sacral nodes, and para-aortic nodes.*

Note
* In the 7th edition the para-aortic nodes were considered to be distant metastatic but to be consistent with advice from FIGO the para-aortic nodes are now classified as regional.

TNM Clinical Classification

T – Primary Tumour

TNM Categories	FIGO Stages	Definition
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumour confined to the cervix[a]

TNM Categories	FIGO Stages	Definition
T1a[b,c]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[d]
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumour without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumour with parametrial invasion
T3	III	Tumour involves lower third of vagina, or extends to pelvic wall, or causes hydronephrosis or non functioning kidney
T3a	IIIA	Tumour involves lower third of vagina
T3b	IIIB	Tumour extends to pelvic wall, or causes hydronephrosis or non functioning kidney
T4	IVA	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis[e]

Notes
[a] Extension to corpus uteri should be disregarded.
[b] The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial papillae to the deepest point of invasion.
[c] All macroscopically visible lesions even with superficial invasion are T1b/IB.
[d] Vascular space involvement, venous or lymphatic, does not affect classification.
[e] Bullous oedema is not sufficient to classify a tumour as T4.

Fig. 1.17 (continued)

N – Regional Lymph Nodes*
NX   Regional lymph nodes cannot be assessed
N0   No regional lymph node metastasis
N1   Regional lymph node metastasis

Note
* No FIGO equivalent.

M – Distant Metastasis
M0   No distant metastasis
M1   Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). It excludes metastasis to vagina, pelvic serosa, and adnexa

pTNM Pathological Classification
The pT and pN categories correspond to the T and N categories.

pN0   Histological examination of a pelvic lymphadenectomy specimen will ordinarily include 10 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pM – Distant Metastasis*
pM1   Distant metastasis microscopically confirmed

Note
* pM0 and pMX are not valid categories.

Stage			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1,T2,T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

FIGO, International Federation of Gynecology and Obstetrics.
Reproduced from Brierley et al. (2017).

TZ varies in its size and its precise position on the cervix, and it may lie partially or completely in the endocervical canal. Determining whether the TZ is fully visible and where it is situated will enable determination of the TZ type (Fig. 1.18). A fully visible ectocervical and small TZ (type 1 TZ) is both easy to assess and simple to treat, either by destruction or by simple excision. In contrast, a large type 3 TZ cannot be assessed completely, and treatment will be associated with greater difficulty, a higher risk of morbidity (Khalid et al., 2011), and an increased risk of failure (Ghaem-Maghami et al., 2007).

Because the TZ is where cervical SCC originates, treatment aims to accomplish eradication of the entire TZ and not only the lesion. Independently of the technique used, ablation to a depth of 7 mm is considered optimal (Shafi et al., 2006); this gives a sufficient degree of safety, because gland crypts containing CIN can be as deep as 4 mm (Anderson & Hartley, 1980).

The choice of the technique to be used depends on the TZ type, the severity and nature of the cervical lesion, the local circumstances, the equipment and training available, and whether general anaesthesia is accessible. Table 1.8 summarizes the treatment options, and the different excision types are illustrated in Fig. 1.18.

(i)   Destructive or ablative methods

With ablative techniques, the TZ epithelium is destroyed rather than preserved, thereby negating the opportunity for histopathological examination; these techniques should not be performed when suspicion of malignancy is high. The most common techniques currently used are cryosurgery (also known as cryocautery, cryotherapy, or cryo) and thermal coagulation (also called thermal ablation or misnamed as cold coagulation). Two other destructive methods are not presented here: radical diathermy, which is no longer used, and laser ablation, which is currently less often used (Monaghan, 1995).

Table 1.4 Stage distribution of cervical cancer using FIGO staging at diagnosis, by country or region and period

Country (territory or region)	Data source	Period of diagnosis	FIGO stage at diagnosis (%)					Reference
			I	II	III	IV	Unknown	
Brazil	Hospital-based cancer registry	2005–2014	21.2	30.7	39.9	8.2	–	Vale et al. (2019)
Canada (Ontario)	Population-based cancer registry	2005–2009	39.8	16.6	14.5	7.0	22	Liu et al. (2016)
Colombia	Hospital-based cancer registry	2007–2012	24.3	21.0	35.2	4.5	15	Pardo & de Vries (2018)
Ethiopia	Hospital or oncology centre	2014–2016	9.9	24.9	40.2	24.9	–	Wassie et al. (2019)
France (Martinique)	Population-based cancer registry	2002–2011	66.7		33.3		–	Melan et al. (2017)
India (Mumbai)	Hospital	2010	13.0	32.0	33.5	6.0	14	Chopra et al. (2018)
Russian Federation (Arkhangelsk)	Population-based cancer registry	2005–2016	39.1	26.1	22.7	12.0	–	Roik et al. (2017)

FIGO, International Federation of Gynecology and Obstetrics.

In the past decade, **cryosurgery** has become very popular as part of a screen-and-treat approach in many low- and middle-income countries (LMICs), but difficulties with maintaining a cheap and reliable supply of carbon dioxide (CO_2) have limited its popularity. Cryosurgery destroys tissue by freezing to below –20 °C, using a metal probe held in close contact with the TZ epithelium. When the method is used for type 1 TZs that are small enough to be completely covered by the probe, success rates are likely to be high. Failure rates are high for lesions that extend to four quadrants of the TZ.

Unlike cryosurgery, which uses cold temperatures to destroy tissue, **thermal coagulation** uses heat. The probe is heated electrically and reaches temperatures of 100–120 °C, which causes intracellular boiling and cell necrosis. It achieves tissue destruction to a depth of 4–7 mm (Haddad et al., 1988). Thermal coagulation has success rates similar to those of cryosurgery, is quicker to perform, has low complication rates, and does not require refrigerated gas. The procedure takes less than 2 minutes to complete and

is usually performed without either general or local anaesthesia; it appears to be well tolerated. Newer thermal coagulation units are battery-operated and can provide sufficient battery power for 30 procedures before recharging is necessary (Pinder et al., 2020). Subsequent pregnancy and fertility rates do not appear to be affected by thermal coagulation.

(ii)   Excisional methods

There are several ways of excising the TZ. These include hysterectomy, cold-knife excision (also known as cold-knife cone biopsy or cold-knife conization), laser cone biopsy, and large loop excision of the transformation zone (LLETZ)/loop electrosurgical excision procedure (LEEP).

Hysterectomy has been widely used to treat suspected or proven cervical precancer. However, hysterectomy should not be used as a treatment of CIN. For women with precancerous lesions, hysterectomy offers no advantage over local excision of the lesion, and for women in whom unsuspected invasive disease is revealed at hysterectomy, the patient will have been poorly served.

Table 1.5 Stage distribution of cervical cancer using three-tiered staging at diagnosis, by country or region and period

Country (region or city)	Data source	Period of diagnosis	Stage at diagnosis (%)[a]				Reference
			Localized	Regional	Distant	Unknown	
Australia (New South Wales)	Population-based cancer registry	2003–2012	41.5, 47.2[b]	34.2, 27.8[b]	17.1, 8.3[b]	7.3, 16.7[b]	Diaz et al. (2018)
Austria	Population-based cancer registry (EUROCARE5)	2000–2007	56	21	7	17	Minicozzi et al. (2017)
Costa Rica	Population-based cancer registry	1995–2000	22.4	40.5	4	33.1	Sankaranarayanan et al. (2011)
Cuba	Population-based cancer registry	1994–1995	41.3	34.3	1.7	22.7	Sankaranarayanan et al. (2011)
Czechia	Population-based cancer registry (EUROCARE5)	2000–2007	61	19	8	12	Minicozzi et al. (2017)
Estonia	Population-based cancer registry (EUROCARE5)	2000–2007	60	26	8	6	Minicozzi et al. (2017)
Finland	Population-based cancer registry (EUROCARE5)	2000–2007	43	5	24	28	Minicozzi et al. (2017)
India (Bhopal)	Population-based cancer registry	1991–1995	28.3	70.5	0.3	0.9	Sankaranarayanan et al. (2011)
India (Chennai)	Population-based cancer registry	1990–1999	6.4	86.0	3.7	3.9	Sankaranarayanan et al. (2011)
India (Karunagappally)	Population-based cancer registry	1991–1997	15.3	60.6	8.8	15.3	Sankaranarayanan et al. (2011)
India (Mumbai)	Population-based cancer registry	1992–1999	27.9	56.8	8.6	6.7	Sankaranarayanan et al. (2011)
Japan (Osaka)	Population-based cancer registry	1976–2012	53	7, 10[c]	10	20	Yagi et al. (2019)
Kuwait	Population-based cancer registry	2000–2013	24.5	36.2	6.1	33.1	Alawadhi et al. (2019)
Norway	Population-based cancer registry	1990–2014	59.6	29.6	8.9	1.9	Thøgersen et al. (2017)
Philippines (Manila)	Population-based cancer registry	1994–1995	21.5	30.5	10.3	37.7	Sankaranarayanan et al. (2011)
Republic of Korea	Nationwide, hospital-based cancer registry	2006–2010	56.4	25.2	6.1	12.4	Jung et al. (2013)
Singapore	Population-based cancer registry	1993–1997	45.5	5.7	5.0	43.8	Sankaranarayanan et al. (2011)
Spain (Basque Country)	Population-based cancer registry (EUROCARE5)	2000–2007	57	30	8	5	Minicozzi et al. (2017)
Spain (Cuenca)	Population-based cancer registry (EUROCARE5)	2000–2007	66	11	20	3	Minicozzi et al. (2017)
Switzerland (St Gallen)	Population-based cancer registry (EUROCARE5)	2000–2007	63	18	12	8	Minicozzi et al. (2017)
Thailand (Chiang Mai)	Population-based cancer registry	1993–1997	26.1	69.7	3.7	0.5	Sankaranarayanan et al. (2011)
Thailand (Chang Mai)	Population-based cancer registry	2008–2012	48	46	5	1	Sripan et al. (2019)

Table 1.5 (continued)

Country (region or city)	Data source	Period of diagnosis	Stage at diagnosis (%)[a]				Reference
			Localized	Regional	Distant	Unknown	
Thailand (Khon Kaen)	Population-based cancer registry	1993–1997	17.3	53.8	6.3	22.6	Sankaranarayanan et al. (2011)
Thailand (Lampang)	Population-based cancer registry	1990–2000	31.2	53.9	5.8	9.2	Sankaranarayanan et al. (2011)
Thailand (Songkhla)	Population-based cancer registry	1990–1999	22.3	54.6	5.8	17.3	Sankaranarayanan et al. (2011)
Turkey (Izmir)	Population-based cancer registry	1995–1997	28.9	41.8	6.1	23.2	Sankaranarayanan et al. (2011)
USA	Population-based cancer registry (SEER)	2004–2009	44.7	35.5	11.5	8.4	Benard et al. (2017)
USA	Population-based cancer registry (SEER)	2014–2016	42	36	17	5	Benard et al. (2019)

EUROCARE, European Cancer Registry-Based Study on Survival and Care of Cancer Patients; SEER, Surveillance, Epidemiology, and End Results Program.

[a] Localized, confined to the cervix and uterus; regional, spread beyond the cervix and uterus to nearby lymph nodes; distant, spread to nearby organs (e.g. bladder or rectum) or distant sites (e.g. lung or bone) (ACS, 2020).

[b] Data are shown for Indigenous and non-Indigenous populations, respectively.

[c] For regional lymph nodes reported separately from adjacent organs.

Table 1.6 Stage-related survival of cervical cancer using FIGO staging at diagnosis, by country or region and period

Country (territory or region)	Data source	Period of diagnosis	FIGO stage at diagnosis (%)					Follow-up	Reference
			I	II	III	IV	Unknown		
India (Mumbai)	Hospital	2010	–	62	45	4	–	5-yr disease-free survival (3-yr for stage IV)	Chopra et al. (2018)
Ethiopia	Hospital or oncology centre	2014–2016	81.04	67.94	23.33	20.03	–	5-yr survival	Wassie et al. (2019)
Colombia	Hospital-based cancer registry	2007–2012	90.3	75.6	47.6	22.6	50.6	2-yr survival	Pardo & de Vries (2018)
France (Martinique)	Population-based cancer registry	2002–2011	71		23		–	5-yr survival	Melan et al. (2017)
Sub-Saharan Africa (excluding Mauritius and Kampala)	Population-based African Cancer Registry Network member registries	2008–2014 (varies between countries)	50.3		20.5		–	5-yr survival	Sengayi-Muchengeti et al. (2020)

FIGO, International Federation of Gynecology and Obstetrics; yr, year.

Table 1.7 Stage-related survival of cervical cancer using three-tiered staging at diagnosis, by country or region and period[a]

Country (region or city)	Period of diagnosis	Stage at diagnosis (%)				Follow-up	Reference
		Localized	Regional	Distant	Unknown		
Costa Rica	1995–2000	89.5	43.1	11.3	43.2	5-yr absolute survival	Sankaranarayanan et al. (2011)
Cuba	1994–1995	73.9	41.5	33.3	45.0	5-yr absolute survival	Sankaranarayanan et al. (2011)
India (Bhopal)	1991–1995	60.6	22.7	0.0	0.0	5-yr absolute survival	Sankaranarayanan et al. (2011)
India (Chennai)	1990–1999	69.1	55.3	12.4	43.4	5-yr absolute survival	Sankaranarayanan et al. (2011)
India (Karunagappally)	1991–1997	72.1	43.5	23.1	44.3	5-yr absolute survival	Sankaranarayanan et al. (2011)
India (Mumbai)	1992–1999	68.3	35.7	2.4	40.7	5-yr absolute survival	Sankaranarayanan et al. (2011)
Japan (Osaka)	2003–2010	90.4	50.3, 59.6[b]	6.9	–	5-yr relative survival	Yagi et al. (2019)
Kuwait	2005–2009	88.4	68.3	–	72.9	5-yr unstandardized net survival	Alawadhi et al. (2019)
Philippines (Manila)	1994–1995	63.1	29.9	7.1	28.2	5-yr absolute survival	Sankaranarayanan et al. (2011)
Republic of Korea[c]	2006–2010	91.1	70.9	25.8	75.1	5-yr survival	Jung et al. (2013)
Singapore	1993–1997	69.7	48.0	20.4	55.7	5-yr absolute survival	Sankaranarayanan et al. (2011)
Thailand (Chiang Mai)	1993–1997	81.2	52.7	12.2	75.0	5-yr absolute survival	Sankaranarayanan et al. (2011)
Thailand (Khon Kaen)	1993–1997	65.1	48.7	30.6	57.0	5-yr absolute survival	Sankaranarayanan et al. (2011)
Thailand (Lampang)	1990–2000	78.7	57.9	6.5	70.6	5-yr absolute survival	Sankaranarayanan et al. (2011)
Thailand (Songkhla)	1990–1999	81.2	56.3	15.4	61.3	5-yr absolute survival	Sankaranarayanan et al. (2011)
Turkey (Izmir)	1995–1997	67.7	54.6	9.3	69.1	5-yr absolute survival	Sankaranarayanan et al. (2011)
USA[d]	2004–2009	85.9	55.8	16.3	56.2	5-yr relative survival	Benard et al. (2017)

yr, year.

[a] Unless otherwise specified, data are from population-based cancer registries.

[b] For regional lymph nodes reported separately from adjacent organs.

[c] Nationwide, hospital-based cancer registry.

[d] Surveillance, Epidemiology, and End Results Program (SEER).

Table 1.8 Treatment options for precancerous lesions of the cervix

Severity and nature of lesion	Treatment options		
	Type 1 TZ	Type 2 TZ	Type 3 TZ
No visible lesion[a]	Ablation	LLETZ Ablation when the TZ does not extend beyond 2 mm inside the endocervical canal	Type 3 excision by LLETZ
Low-grade or high-grade squamous lesions[b]	Ablation (preferred in a screen-and-treat setting or for low-grade lesions) LLETZ	LLETZ Ablation when the TZ does not extend beyond 2 mm inside the endocervical canal	Type 3 excision by LLETZ using a sufficiently long loop, or top-hat excision, SWETZ, or NETZ; CKC (only if the electrosurgical techniques are not feasible)
Glandular lesions[c]	Type 3 excision with CKC, SWETZ or NETZ, followed by endocervical curetting LLETZ with a sufficiently long loop, if the other techniques are not feasible		
Microinvasive cancer[d]	Type 3 excision with CKC, SWETZ, or NETZ, followed by endocervical curetting		

CKC, cold-knife conization; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LLETZ, large loop excision of the transformation zone; NETZ, needle excision of the transformation zone; SWETZ, straight wire excision of the transformation zone; TZ, transformation zone; VIA, visual inspection with acetic acid.

[a] HPV-positive women in a screen-and-treat setting; cytology suspecting HSIL or glandular abnormalities.

[b] Abnormal VIA in a screen-and-treat setting, colposcopically suspected or histopathologically proved.

[c] Cytology suspecting glandular lesion, suspicion of glandular abnormalities on colposcopy, or adenocarcinoma in situ confirmed on histopathology.

[d] Early invasive cancer suspected on colposcopy although histopathology shows less severe abnormality; microinvasive cancer confirmed on histopathology.

After a simple hysterectomy, it is not possible to offer the appropriate radiotherapy regime, and radical hysterectomy is also not possible.

Cold-knife conization, the oldest method of local excision, is still widely used, especially where colposcopy facilities and/or expertise are not available. The technique leaves a relatively large cervical defect and often removes more tissue than is necessary. The procedure is usually performed under general anaesthesia. A suture or sutures are often used to achieve post-excision haemostasis. Cold-knife conization is associated with well-recognized short- and long-term complications, including primary and secondary haemorrhage, cervical stenosis, and cervical incompetence. It may be selected for glandular or microinvasive disease, but otherwise cold-knife conization has no advantages over LLETZ/LEEP or laser excision and is associated with greater morbidity and long-term pregnancy-related com-

plications (Jones et al., 1979; Kristensen et al., 1993; Arbyn et al., 2008).

LLETZ/LEEP involves excision of the TZ using a low-voltage diathermy loop of thin wire, usually with blended diathermy under local anaesthesia. This technique is used for a type 1 excision (Fig. 1.18) and is appropriate for most women with CIN (i.e. for a small or medium-sized type 1 TZ). It leads to the excision of the entire TZ and only the TZ, to a depth of about 5–7 mm, and the diathermy artefactual damage of the loop will cause necrosis for a further 2–3 mm. Short-term complications after LLETZ include light vaginal bleeding, mild discomfort, and a little discharge.

Alternative electrosurgery techniques for an endocervical TZ. Although type 3 excisions, especially large ones, are known to be associated with an increase in the risk of subsequent pregnancy-related complications (primarily premature delivery) (Khalid et al., 2012), a type 3

Fig. 1.18 Determination of the transformation zone (TZ) types of the cervix, and TZ excision types

Type 1 TZ

Mature native squamous epithelium

Columnar epithelium

Transformation zone

Upper limit of visibility

Columnar epithelium

Mature native squamous epithelium

Upper limit of visibility

Transformation zone

Type 2 TZ

Squamous epithelium

Columnar epithelium

Transformation zone

Upper limit of visibility

Columnar epithelium

Mature native squamous epithelium

Upper limit of visibility

Transformation zone

Type 3 TZ

Native mature squamous epithelium

Transformation zone

Upper limit of visibility

Columnar epithelium

Mature native squamous epithelium

Upper limit of visibility

Transformation zone

A type 1 TZ is completely ectocervical, is fully visible, and may be small or large. A type 2 TZ has an endocervical component but is still fully visible. The ectocervical component may be small or large. A type 3 TZ has an endocervical component, and the upper limit is not fully visible. The ectocervical component, if present, may be small or large. The dotted green lines represent the TZ excision types. Type 1 and type 2 excisions relate exactly to the corresponding TZ types. In contrast, a type 3 excision may also be used in several circumstances not dictated purely by the TZ type (e.g. for glandular lesions) (see Table 1.8). Adapted from Prendiville & Sankaranarayanan (2017). Courtesy of Walter Prendiville, with permission.

excision is sometimes necessary, for example for a type 3 TZ with suspected high-grade SIL, glandular disease, or even suspected microinvasion. A type 3 excision may require general anaesthesia, depending on how large and how long the excision needs to be, access to the cervix, and patient compliance. Alternative techniques to LLETZ use a straight wire (SWETZ; Russomano et al., 2015) or a needle (NETZ). Top-hat LEEP involves two steps of loop excision: a conventional LEEP followed by a second excision of the residual endocervix using a smaller-diameter loop. Given the greater extent of endocervical excision compared with conventional LEEP, top-hat LEEP may reduce the risk of incomplete endocervical excision in women with a type 3 TZ (Kietpeerakool et al., 2010).

(iii) Follow-up after treatment of squamous precancerous lesions

Because treatment methods are not associated with a 100% success rate, it is important to establish a follow-up protocol to identify the small percentage (< 10%) of women treated who will have residual CIN. Women who have been treated for cervical precancer are much more likely to develop cervical cancer. This increased risk has been quantified as being 2–5 times the background risk, and much of it is a result of poor long-term follow-up (Soutter et al., 1997; Strander et al., 2007). Several case series of cervical cancer have demonstrated that more than 50% of cancers occur in women who are lost to follow-up (Ghaem-Maghami et al., 2007) and that this increase in risk lasts for 20 years or more.

(b) Treatment of adenocarcinoma in situ

AIS is a precursor of invasive adenocarcinoma. Colposcopic assessment of glandular dysplasia is less reliable than that of squamous disease. Most glandular disease has an endocervical component, and it is often not possible to determine the extent of endocervical involvement of dysplastic epithelium in the endocervical canal. Therefore, destructive techniques are contraindicated. The definitive management of glandular dysplasia is excision of the TZ and a proportion of full-thickness endocervical canal epithelium. It is crucial that the pathologist has sufficient undamaged tissue with which to make a diagnosis and assess margin involvement. A cylindrical type 3 excision should be performed using a straight wire, cold knife, or laser. Such conservative management of AIS is justified in a young woman who is assured of adequate follow-up until she has completed her family, when hysterectomy should be considered.

(c) Treatment of invasive cervical cancer

In general, early cervical cancer (SCC or adenocarcinoma) is treated using surgical excision with simple or radical hysterectomy and pelvic lymph node evaluation, whereas advanced cervical cancer is treated with concurrent chemotherapy and radiation. Fertility-sparing surgical procedures such as conization or trachelectomy can also be offered to women who have not completed their family. Detailed information can be found elsewhere (e.g. WHO, 2014; Buchanan et al., 2017; Prendiville & Sankaranarayanan, 2017; Cancer Research UK, 2020; Nica et al., 2021).

References

ACS (2020). Early detection, diagnosis, and staging. Survival rates for cervical cancer. Atlanta (GA), USA: American Cancer Society. Available from: https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/survival.html.

Adegoke O, Kulasingam S, Virnig B (2012). Cervical cancer trends in the United States: a 35-year population-based analysis. *J Womens Health (Larchmt)*. 21(10):1031–7. doi:10.1089/jwh.2011.3385 PMID:22816437

Alawadhi E, Al-Awadi A, Elbasmi A, Coleman MP, Allemani C (2019). Cancer survival by stage at diagnosis in Kuwait: a population-based study.

J Oncol. 2019:8463195. doi:10.1155/2019/8463195 PMID:31662756

Allemani C (2017). The importance of global surveillance of cancer survival for cancer control: the CONCORD programme. *Cancer Control.* 2017:19–22. Available from: http://www.cancercontrol.info/2017-3/the-importance-of-global-surveillance-of-cancer-survival-for-cancer-control-the-concord-programme/.

Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al.; CONCORD Working Group (2018). Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet.* 391(10125):1023–75. doi:10.1016/S0140-6736(17)33326-3 PMID:29395269

Anderson MC, Hartley RB (1980). Cervical crypt involvement by intraepithelial neoplasia. *Obstet Gynecol.* 55(5):546–50. PMID:7366912

Anonymous (2019). Corrigendum to "Revised FIGO staging for carcinoma of the cervix uteri" [Int J Gynecol Obstet 145(2019) 129–135]. *Int J Gynaecol Obstet.* 147(2):279–80. doi:10.1002/ijgo.12969 PMID:31571232

Arbyn M, Kyrgiou M, Simoens C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. (2008). Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ.* 337:a1284. doi:10.1136/bmj.a1284 PMID:18801868

Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. (2020). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health.* 8(2):e191–203. doi:10.1016/S2214-109X(19)30482-6 PMID:31812369

Benard VB, Greek A, Jackson JE, Senkomago V, Hsieh MC, Crosbie A, et al. (2019). Overview of Centers for Disease Control and Prevention's Case Investigation of Cervical Cancer Study. *J Womens Health (Larchmt).* 28(7):890–6. doi:10.1089/jwh.2019.7849 PMID:31264934

Benard VB, Watson M, Saraiya M, Harewood R, Townsend JS, Stroup AM, et al. (2017). Cervical cancer survival in the United States by race and stage (2001–2009): findings from the CONCORD-2 study. *Cancer.* 123(Suppl 24):5119–37. doi:10.1002/cncr.30906 PMID:29205300

Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R (2018). Cancer of the cervix uteri. *Int J Gynaecol Obstet.* 143(Suppl 2):22–36. doi:10.1002/ijgo.12611 PMID:30306584

Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, et al. (2019). Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet.* 145(1):129–35. doi:10.1002/ijgo.12749 PMID:30656645

Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al.; WHO International Agency for Research on Cancer Monograph Working Group (2009). A review of human carcinogens – Part B: biological agents. *Lancet Oncol.* 10(4):321–2. doi:10.1016/S1470-2045(09)70096-8 PMID:19350698

Bray F, Carstensen B, Møller H, Zappa M, Zakelj MP, Lawrence G, et al. (2005). Incidence trends of adenocarcinoma of the cervix in 13 European countries. *Cancer Epidemiol Biomarkers Prev.* 14(9):2191–9. doi:10.1158/1055-9965.EPI-05-0231 PMID:16172231

Brierley JD, Gospodarowicz MK, Wittekind C, editors (2017). TNM classification of malignant tumours. 8th ed. Hoboken, NJ (USA): Wiley Blackwell.

Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. (2020). Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet.* 395(10224):575–90. doi:10.1016/S0140-6736(20)30068-4 PMID:32007141

Bruni L, Serrano B, Diaz Sanchis M, Bosch José FX, de Sanjosé Llongueras S (2016). Update of global estimates of HPV prevalence: meta-analysis of 2.4 million women with normal cytology. Presented at International Papillomavirus Conference, Sydney, Australia.

Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, de Sanjosé S (2010). Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *J Infect Dis.* 202(12):1789–99. doi:10.1086/657321 PMID:21067372

Buchanan T, Pierce JY, Graybill W, Kohler M, Creasman W (2017). Why do we continue to overtreat stage Ia carcinoma of the cervix? *Am J Obstet Gynecol.* 217(4):413–7. doi:10.1016/j.ajog.2017.05.020 PMID:28522321

Burk RD, Harari A, Chen Z (2013). Human papillomavirus genome variants. *Virology.* 445(1–2):232–43. doi:10.1016/j.virol.2013.07.018 PMID:23998342

Bzhalava D, Eklund C, Dillner J (2015). International standardization and classification of human papillomavirus types. *Virology.* 476:341–4. doi:10.1016/j.virol.2014.12.028 PMID:25577151

Campos NG, Demarco M, Bruni L, Desai KT, Gage JC, Adebamowo SN, et al. (2021). A proposed new generation of evidence-based microsimulation models to inform global control of cervical cancer. *Prev Med.* 144:106438. doi:10.1016/j.ypmed.2021.106438 PMID:33678235

Cancer Research UK (2020). Treatment for cervical cancer. Oxford, UK: Cancer Research UK. Available from: https://www.cancerresearchuk.org/about-cancer/cervical-cancer/treatment.

Cantor SB, Atkinson EN, Cardenas-Turanzas M, Benedet JL, Follen M, MacAulay C (2005). Natural history of cervical intraepithelial neoplasia: a meta-analysis. *Acta Cytol.* 49(4):405–15. doi:10.1159/000326174 PMID:16124170

Castle PE, Adcock R, Cuzick J, Wentzensen N, Torrez-Martinez NE, Torres SM, et al.; New Mexico HPV Pap Registry Steering Committee; p16 IHC Study

Panel (2020). Relationships of p16 immunohistochemistry and other biomarkers with diagnoses of cervical abnormalities: implications for LAST terminology. *Arch Pathol Lab Med*. 144(6):725–34. doi:10.5858/arpa.2019-0241-OA PMID:31718233

Castle PE, Jeronimo J, Schiffman M, Herrero R, Rodríguez AC, Bratti MC, et al. (2006). Age-related changes of the cervix influence human papillomavirus type distribution. *Cancer Res*. 66(2):1218–24. doi:10.1158/0008-5472.CAN-05-3066 PMID:16424061

Castle PE, Kinney WK, Cheung LC, Gage JC, Fetterman B, Poitras NE, et al. (2017). Why does cervical cancer occur in a state-of-the-art screening program? *Gynecol Oncol*. 146(3):546–53. doi:10.1016/j.ygyno.2017.06.003 PMID:28606721

Castle PE, Pierz A, Stoler MH (2018). A systematic review and meta-analysis on the attribution of human papillomavirus (HPV) in neuroendocrine cancers of the cervix. *Gynecol Oncol*. 148(2):422–9. doi:10.1016/j.ygyno.2017.12.001 PMID:29248196

Chen Z, Schiffman M, Herrero R, DeSalle R, Anastos K, Segondy M, et al. (2018). Classification and evolution of human papillomavirus genome variants: Alpha-5 (HPV26, 51, 69, 82), Alpha-6 (HPV30, 53, 56, 66), Alpha-11 (HPV34, 73), Alpha-13 (HPV54) and Alpha-3 (HPV61). *Virology*. 516:86–101. doi:10.1016/j.virol.2018.01.002 PMID:29331867

Chopra S, Gupta M, Mathew A, Mahantshetty U, Engineer R, Lavanya G, et al. (2018). Locally advanced cervical cancer: a study of 5-year outcomes. *Indian J Cancer*. 55(1):45–9. doi:10.4103/ijc.IJC_428_17 PMID:30147092

Combes J-D, Guan P, Franceschi S, Clifford GM (2015). Judging the carcinogenicity of rare human papillomavirus types. *Int J Cancer*. 136(3):740–2. doi:10.1002/ijc.29019 PMID:24917192

Cullen M, Boland JF, Schiffman M, Zhang X, Wentzensen N, Yang Q, et al. (2015). Deep sequencing of HPV16 genomes: a new high-throughput tool for exploring the carcinogenicity and natural history of HPV16 infection. *Papillomavirus Res*. 1:3–11. doi:10.1016/j.pvr.2015.05.004 PMID:26645052

Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al.; Members of LAST Project Work Groups (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. [Erratum in: Arch Pathol Lab Med. 2013 137(6):738] *Arch Pathol Lab Med*. 136(10):1266–97. doi:10.5858/arpa.LGT200570 PMID:22742517

de Martel C, Plummer M, Vignat J, Franceschi S (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 141(4):664–70. doi:10.1002/ijc.30716 PMID:28369882

de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al.; Retrospective International Survey and HPV Time Trends Study Group (2010). Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol*. 11(11):1048–56. doi:10.1016/S1470-2045(10)70230-8 PMID:20952254

de Sanjosé S, Serrano B, Tous S, Alejo M, Lloveras B, Quirós B, et al.; RIS HPV TT, VVAP and Head and Neck study groups (2018). Burden of human papillomavirus (HPV)-related cancers attributable to HPVs 6/11/16/18/31/33/45/52 and 58. *JNCI Cancer Spectr*. 2(4):pky045. doi:10.1093/jncics/pky045 PMID:31360870

Demarco M, Hyun N, Carter-Pokras O, Raine-Bennett TR, Cheung L, Chen X, et al. (2020). A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. *EClinicalMedicine*. 22:100293. doi:10.1016/j.eclinm.2020.100293 PMID:32510043

Dhillon PK, Yeole BB, Dikshit R, Kurkure AP, Bray F (2011). Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976–2005: an age-period-cohort analysis. *Br J Cancer*. 105(5):723–30. doi:10.1038/bjc.2011.301 PMID:21829198

Diaz A, Baade PD, Valery PC, Whop LJ, Moore SP, Cunningham J, et al. (2018). Comorbidity and cervical cancer survival of Indigenous and non-Indigenous Australian women: a semi-national registry-based cohort study (2003–2012). *PLoS One*. 13(5):e0196764. doi:10.1371/journal.pone.0196764 PMID:29738533

Doorbar J (2018). Host control of human papillomavirus infection and disease. *Best Pract Res Clin Obstet Gynaecol*. 47:27–41. doi:10.1016/j.bpobgyn.2017.08.001 PMID:28919159

Doorbar J, Griffin H (2019). Refining our understanding of cervical neoplasia and its cellular origins. *Papillomavirus Res*. 7:176–9. doi:10.1016/j.pvr.2019.04.005 PMID:30974183

Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. (2012). The biology and life-cycle of human papillomaviruses. *Vaccine*. 30(Suppl 5):F55–70. doi:10.1016/j.vaccine.2012.06.083 PMID:23199966

Ferlay J, Colombet M, Bray F (2018). Cancer incidence in five continents, CI5*plus*: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from: https://ci5.iarc.fr/CI5plus.

Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Pineros M, et al. (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today.

Fox H, Buckley H, Al-Nafussi A, et al. (1999). Histopathology reporting in cervical screening. 1st ed. Sheffield, UK: NHS Cervical Screening Programme.

Gage JC, Schiffman M, Katki HA, Castle PE, Fetterman B, Wentzensen N, et al. (2014). Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J Natl Cancer Inst.* 106(8):dju153. doi:10.1093/jnci/dju153 PMID:25038467

García-Vallvé S, Alonso A, Bravo IG (2005). Papillomaviruses: different genes have different histories. *Trends Microbiol.* 13(11):514–21. doi:10.1016/j.tim.2005.09.003 PMID:16181783

Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP (2007). Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol.* 8(11):985–93. doi:10.1016/S1470-2045(07)70283-8 PMID:17928267

Gibbs J, Mei S, Economos K, Lee YC, Kanis MJ (2019). Clinicopathologic features, incidence, and survival trends of gynecologic neuroendocrine tumors: a SEER database analysis. *Am J Obstet Gynecol.* 221(1):53.e1–6. doi:10.1016/j.ajog.2019.02.052 PMID:30849352

Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, et al. (2017). The global burden of women's cancers: a grand challenge in global health. *Lancet.* 389(10071):847–60. doi:10.1016/S0140-6736(16)31392-7 PMID:27814965

González P, Hildesheim A, Rodríguez AC, Schiffman M, Porras C, Wacholder S, et al. (2010). Behavioral/lifestyle and immunologic factors associated with HPV infection among women older than 45 years. *Cancer Epidemiol Biomarkers Prev.* 19(12):3044–54. doi:10.1158/1055-9965.EPI-10-0645 PMID:20952561

Gravitt PE, Marks M, Kosek M, Huang C, Cabrera L, Olortegui MP, et al. (2016). Soil-transmitted helminth infections are associated with an increase in human papillomavirus prevalence and a T-helper type 2 cytokine signature in cervical fluids. *J Infect Dis.* 213(5):723–30. doi:10.1093/infdis/jiv498 PMID:26486638

Griffin H, Soneji Y, Van Baars R, Arora R, Jenkins D, van de Sandt M, et al. (2015). Stratification of HPV-induced cervical pathology using the virally encoded molecular marker E4 in combination with p16 or MCM. *Mod Pathol.* 28(7):977–93. doi:10.1038/modpathol.2015.52 PMID:25953390

Grigsby PW, Massad LS, Mutch DG, Powell MA, Thaker PH, McCourt C, et al. (2020). FIGO 2018 staging criteria for cervical cancer: impact on stage migration and survival. *Gynecol Oncol.* 157(3):639–43. doi:10.1016/j.ygyno.2020.03.027 PMID:32248993

Guan P, Clifford GM, Franceschi S (2013). Human papillomavirus types in glandular lesions of the cervix: a meta-analysis of published studies. *Int J Cancer.* 132(1):248–50. doi:10.1002/ijc.27663 PMID:22684765

Guan P, Howell-Jones R, Li N, Bruni L, de Sanjosé S, Franceschi S, et al. (2012). Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *Int J Cancer.* 131(10):2349–59. doi:10.1002/ijc.27485 PMID:22323075

Haddad N, Hussein I, Blessing K, Kerr-Wilson R, Smart G (1988). Tissue destruction following cold coagulation of the cervix. *J Gynecol Surg.* 4(1):23–7. doi:10.1089/gyn.1988.4.23

Hirschowitz L, Albus A, Brown C, Das N, Ganesan R, Herrington CS, et al. (2012). Histopathology reporting in cervical screening – an integrated approach. 2nd ed. Sheffield, UK: NHS Cervical Screening Programme.

Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD (1998). Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med.* 338(7):423–8. doi:10.1056/NEJM199802123380703 PMID:9459645

Hodgson A, Olkhov-Mitsel E, Howitt BE, Nucci MR, Parra-Herran C (2019). International Endocervical Adenocarcinoma Criteria and Classification (IECC): correlation with adverse clinicopathological features and patient outcome. *J Clin Pathol.* 72(5):347–53. doi:10.1136/jclinpath-2018-205632 PMID:30679193

IARC (2012). Biological agents. *IARC Monogr Eval Carcinog Risks Hum.* 100B:1–475. Available from: https://publications.iarc.fr/119 PMID:23189750

Islami F, Fedewa SA, Jemal A (2019). Trends in cervical cancer incidence rates by age, race/ethnicity, histological subtype, and stage at diagnosis in the United States. *Prev Med.* 123:316–23. doi:10.1016/j.ypmed.2019.04.010 PMID:31002830

Jedy-Agba E, Joko WY, Liu B, Buziba NG, Borok M, Korir A, et al. (2020). Trends in cervical cancer incidence in sub-Saharan Africa. *Br J Cancer.* 123(1):148–54. doi:10.1038/s41416-020-0831-9 PMID:32336751

Jones JM, Sweetnam P, Hibbard BM (1979). The outcome of pregnancy after cone biopsy of the cervix: a case-control study. *Br J Obstet Gynaecol.* 86(12):913–6. doi:10.1111/j.1471-0528.1979.tb11237.x PMID:575050

Jung KW, Won YJ, Kong HJ, Oh CM, Shin A, Lee JS (2013). Survival of Korean adult cancer patients by stage at diagnosis, 2006–2010: national cancer registry study. *Cancer Res Treat.* 45(3):162–71. doi:10.4143/crt.2013.45.3.162 PMID:24155674

Kawauchi S, Kusuda T, Liu XP, Suehiro Y, Kaku T, Mikami Y, et al. (2008). Is lobular endocervical glandular hyperplasia a cancerous precursor of minimal deviation adenocarcinoma?: a comparative molecular-genetic and immunohistochemical study. *Am J Surg Pathol.* 32(12):1807–15. doi:10.1097/PAS.0b013e3181883722 PMID:18779726

Khalid S, Carcopino X, Michail G, Metchette S, Conroy R, Prendiville W (2011). Compliance with follow up cytology after discharge from the colposcopy clinic. *Ir Med J.* 104(6):167–70. PMID:22111391

Khalid S, Dimitriou E, Conroy R, Paraskevaidis E, Kyrgiou M, Harrity C, et al. (2012). The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. *BJOG.* 119(6):685–91. doi:10.1111/j.1471-0528.2011.03252.x PMID:22329499

Kietpeerakool C, Suprasert P, Khunamornpong S, Sukpan K, Settakorn J, Srisomboon J (2010). "Top hat" versus conventional loop electrosurgical excision procedure in women with a type 3 transformation zone. *Int J Gynaecol Obstet*. 109(1):59–62. doi:10.1016/j.ijgo.2009.11.005 PMID:20022598

Kjaer SK, Dahl C, Engholm G, Bock JE, Lynge E, Jensen OM (1992). Case-control study of risk factors for cervical neoplasia in Denmark. II. Role of sexual activity, reproductive factors, and venereal infections. *Cancer Causes Control*. 3(4):339–48. doi:10.1007/BF00146887 PMID:1617121

Klaes R, Benner A, Friedrich T, Ridder R, Herrington S, Jenkins D, et al. (2002). p16INK4a immunohistochemistry improves interobserver agreement in the diagnosis of cervical intraepithelial neoplasia. *Am J Surg Pathol*. 26(11):1389–99. doi:10.1097/00000478-200211000-00001 PMID:12409715

Klaes R, Friedrich T, Spitkovsky D, Ridder R, Rudy W, Petry U, et al. (2001). Overexpression of p16INK4A as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. *Int J Cancer*. 92(2):276–84. doi:10.1002/ijc.1174 PMID:11291057

Kojima A, Mikami Y, Sudo T, Yamaguchi S, Kusanagi Y, Ito M, et al. (2007). Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am J Surg Pathol*. 31(5):664–72. doi:10.1097/01.pas.0000213434.91868.b0 PMID:17460448

Kristensen J, Langhoff-Roos J, Kristensen FB (1993). Increased risk of preterm birth in women with cervical conization. *Obstet Gynecol*. 81(6):1005–8. PMID:8497340

Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors (2014). WHO classification of tumours of female reproductive organs. 4th ed. Lyon, France: International Agency for Research on Cancer.

Kusanagi Y, Kojima A, Mikami Y, Kiyokawa T, Sudo T, Yamaguchi S, et al. (2010). Absence of high-risk human papillomavirus (HPV) detection in endocervical adenocarcinoma with gastric morphology and phenotype. *Am J Pathol*. 177(5):2169–75. doi:10.2353/ajpath.2010.100323 PMID:20829441

Lei J, Andrae B, Ploner A, Lagheden C, Eklund C, Nordqvist Kleppe S, et al. (2019). Cervical screening and risk of adenosquamous and rare histological types of invasive cervical carcinoma: population based nested case-control study. *BMJ*. 365:l1207. doi:10.1136/bmj.l1207 PMID:30944091

Li X, Zheng R, Li X, Shan H, Wu Q, Wang Y, et al. (2017). Trends of incidence rate and age at diagnosis for cervical cancer in China, from 2000 to 2014. *Chin J Cancer Res*. 29(6):477–86. doi:10.21147/j.issn.1000-9604.2017.06.02 PMID:29353970

Liu N, Mittmann N, Coyte PC, Hancock-Howard R, Seung SJ, Earle CC (2016). Phase-specific healthcare costs of cervical cancer: estimates from a population-based study. *Am J Obstet Gynecol*. 214(5):615.e1–11. doi:10.1016/j.ajog.2015.11.021 PMID:26627729

Lorincz AT, Brentnall AR, Vasiljević N, Scibior-Bentkowska D, Castanon A, Fiander A, et al. (2013). HPV16 L1 and L2 DNA methylation predicts high-grade cervical intraepithelial neoplasia in women with mildly abnormal cervical cytology. *Int J Cancer*. 133(3):637–44. doi:10.1002/ijc.28050 PMID:23335178

Malagón T, Louvanto K, Wissing M, Burchell AN, Tellier PP, El-Zein M, et al. (2019). Hand-to-genital and genital-to-genital transmission of human papillomaviruses between male and female sexual partners (HITCH): a prospective cohort study. *Lancet Infect Dis*. 19(3):317–26. doi:10.1016/S1473-3099(18)30655-8 PMID:30745276

Matsuo K, Machida H, Mandelbaum RS, Konishi I, Mikami M (2019). Validation of the 2018 FIGO cervical cancer staging system. *Gynecol Oncol*. 152(1):87–93. doi:10.1016/j.ygyno.2018.10.026 PMID:30389105

Maucort-Boulch D, Plummer M, Castle PE, Demuth F, Safaeian M, Wheeler CM, et al. (2010). Predictors of human papillomavirus persistence among women with equivocal or mildly abnormal cytology. *Int J Cancer*. 126(3):684–91. doi:10.1002/ijc.24752 PMID:19609952

McCluggage WG (2016). Recent developments in non-HPV-related adenocarcinomas of the lower female genital tract and their precursors. *Adv Anat Pathol*. 23(1):58–69. doi:10.1097/PAP.0000000000000095 PMID:26645463

McCredie MRE, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. (2008). Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*. 9(5):425–34. doi:10.1016/S1470-2045(08)70103-7 PMID:18407790

Melan K, Janky E, Macni J, Ulric-Gervaise S, Dorival MJ, Veronique-Baudin J, et al. (2017). Epidemiology and survival of cervical cancer in the French West-Indies: data from the Martinique Cancer Registry (2002–2011). *Glob Health Action*. 10(1):1337341. doi:10.1080/16549716.2017.1337341 PMID:28649938

Mikami Y (2020). Gastric-type mucinous carcinoma of the cervix and its precursors – historical overview. *Histopathology*. 76(1):102–11. doi:10.1111/his.13993 PMID:31846534

Minicozzi P, Innos K, Sánchez MJ, Trama A, Walsh PM, Marcos-Gragera R, et al.; EUROCARE-5 Working Group (2017). Quality analysis of population-based information on cancer stage at diagnosis across Europe, with presentation of stage-specific cancer survival estimates: a EUROCARE-5 study. *Eur J Cancer*. 84:335–53. doi:10.1016/j.ejca.2017.07.015 PMID:28865261

Monaghan JM (1995). Laser vaporization and excisional techniques in the treatment of cervical intraepithelial neoplasia. *Baillieres Clin Obstet Gynaecol*. 9(1):173–87. doi:10.1016/S0950-3552(05)80365-7 PMID:7600726

Nica A, Marchocki Z, Gien LT, Kupets R, Vicus D, Covens A (2021). Cervical conization and lymph node assessment for early stage low-risk cervical cancer. *Int J Gynecol Cancer*. 31(3):447–51. doi:10.1136/ijgc-2020-001785 PMID:33649012

Nicolás I, Marimon L, Barnadas E, Saco A, Rodríguez-Carunchio L, Fusté P, et al. (2019). HPV-negative tumors of the uterine cervix. *Mod Pathol*. 32(8):1189–96. doi:10.1038/s41379-019-0249-1 PMID:30911077

Nishio S, Mikami Y, Tokunaga H, Yaegashi N, Satoh T, Saito M, et al. (2019). Analysis of gastric-type mucinous carcinoma of the uterine cervix – an aggressive tumor with a poor prognosis: a multi-institutional study. *Gynecol Oncol*. 153(1):13–9. doi:10.1016/j.ygyno.2019.01.022 PMID:30709650

Ojamaa K, Innos K, Baburin A, Everaus H, Veerus P (2018). Trends in cervical cancer incidence and survival in Estonia from 1995 to 2014. *BMC Cancer*. 18(1):1075. doi:10.1186/s12885-018-5006-1 PMID:30404606

Ostör AG (1993). Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol*. 12(2):186–92. doi:10.1097/00004347-199304000-00018 PMID:8463044

Pardo C, de Vries E (2018). Breast and cervical cancer survival at Instituto Nacional de Cancerología, Colombia. *Colomb Med (Cali)*. 49(1):102–8. doi:10.25100/cm.v49i1.2840 PMID:29983470

Pecorelli S, Zigliani L, Odicino F (2009). Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet*. 105(2):107–8. doi:10.1016/j.ijgo.2009.02.009 PMID:19342051

Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al.; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee (2020). 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Low Genit Tract Dis*. 24(2):102–31. doi:10.1097/LGT.0000000000000525 PMID:32243307

Perme MP, Stare J, Estève J (2012). On estimation in relative survival. *Biometrics*. 68(1):113–20. doi:10.1111/j.1541-0420.2011.01640.x PMID:21689081

Petry KU, Scholz U, Hollwitz B, Von Wasielewski R, Meijer CJ (2003). Human papillomavirus, coinfection with *Schistosoma hematobium*, and cervical neoplasia in rural Tanzania. *Int J Gynecol Cancer*. 13(4):505–9. doi:10.1136/ijgc-00009577-200307000-00015 PMID:12911728

Pinder LF, Parham GP, Basu P, Muwonge R, Lucas E, Nyambe N, et al. (2020). Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial. *Lancet Oncol*. 21(1):175–84. doi:10.1016/S1470-2045(19)30635-7 PMID:31734069

Pinheiro M, Gage JC, Clifford GM, Demarco M, Cheung LC, Chen Z, et al. (2020). Association of HPV35 with cervical carcinogenesis among women of African ancestry: evidence of viral-host interaction with implications for disease intervention. *Int J Cancer*. 147(10):2677–86. doi:10.1002/ijc.33033 PMID:32363580

Plummer M, Schiffman M, Castle PE, Maucort-Boulch D, Wheeler CM; ALTS Group (2007). A 2-year prospective study of human papillomavirus persistence among women with a cytological diagnosis of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. *J Infect Dis*. 195(11):1582–9. doi:10.1086/516784 PMID:17471427

Prendiville W, Sankaranarayanan R (2017). Colposcopy and treatment of cervical precancer (IARC Technical Publications, No. 45). Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/555.

Quint WG, Scholte G, van Doorn LJ, Kleter B, Smits PH, Lindeman J (2001). Comparative analysis of human papillomavirus infections in cervical scrapes and biopsy specimens by general SPF$_{10}$ PCR and HPV genotyping. *J Pathol*. 194(1):51–8. doi:10.1002/path.855 PMID:11329141

Reagan JW, Seidemann IL, Saracusa Y (1953). The cellular morphology of carcinoma in situ and dysplasia or atypical hyperplasia of the uterine cervix. *Cancer*. 6(2):224–34. doi:10.1002/1097-0142(195303)6:2<224::AID-CNCR2820060203>3.0.CO;2-H PMID:13032911

Richart RM (1967). Natural history of cervical intraepithelial neoplasia. *Clin Obstet Gynecol*. 10(4):748–84. doi:10.1097/00003081-196712000-00002 PMID:4172733

Rodríguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, et al. (2010). Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst*. 102(5):315–24. doi:10.1093/jnci/djq001 PMID:20157096

Rodríguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, et al. (2012). Low risk of type-specific carcinogenic HPV re-appearance with subsequent cervical intraepithelial neoplasia grade 2/3. *Int J Cancer*. 131(8):1874–81. doi:10.1002/ijc.27418 PMID:22213126

Rodríguez-Carunchio L, Soveral I, Steenbergen RD, Torné A, Martinez S, Fusté P, et al. (2015). HPV-negative carcinoma of the uterine cervix: a distinct type of cervical cancer with poor prognosis. *BJOG*. 122(1):119–27. doi:10.1111/1471-0528.13071 PMID:25229645

Rohner E, Bütikofer L, Schmidlin K, Sengayi M, Maskew M, Giddy J, et al. (2020). Cervical cancer risk in women living with HIV across four continents: a multicohort

study. *Int J Cancer*. 146(3):601–9. doi:10.1002/ijc.32260 PMID:31215037

Roik EE, Nieboer E, Kharkova OA, Grjibovski AM, Postoev VA, Odland JØ (2017). Do cervical cancer patients diagnosed with opportunistic screening live longer? An Arkhangelsk Cancer Registry study. *Int J Environ Res Public Health*. 14(12):1500. doi:10.3390/ijerph14121500 PMID:29186874

Russomano F, Tristao MA, Côrtes R, de Camargo MJ (2015). A comparison between type 3 excision of the transformation zone by straight wire excision of the transformation zone (SWETZ) and large loop excision of the transformation zone (LLETZ): a randomized study. *BMC Womens Health*. 15(1):12. doi:10.1186/s12905-015-0174-5 PMID:25783647

Ryser MD, Rositch A, Gravitt PE (2017). Modeling of US human papillomavirus (HPV) seroprevalence by age and sexual behavior indicates an increasing trend of HPV infection following the sexual revolution. *J Infect Dis*. 216(5):604–11. doi:10.1093/infdis/jix333 PMID:28931221

Sankaranarayanan R, Swaminathan R, Lucas E (2011). Cancer survival in Africa, Asia, the Caribbean and Central America (IARC Scientific Publications, No. 162). Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/317.

Schiffman, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S (2007). Human papillomavirus and cervical cancer. *Lancet*. 370(9590):890–907. doi:10.1016/S0140-6736(07)61416-0 PMID:17826171

Schiffman M, Castle PE (2005). The promise of global cervical-cancer prevention. *N Engl J Med*. 353(20): 2101–4. doi:10.1056/NEJMp058171 PMID:16291978

Schiffman M, Clifford G, Buonaguro FM (2009). Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. *Infect Agent Cancer*. 4(1):8. doi:10.1186/1750-9378-4-8 PMID:19486508

Schiffman M, de Sanjose S (2019). False positive cervical HPV screening test results. *Papillomavirus Res*. 7:184–7. doi:10.1016/j.pvr.2019.04.012 PMID:31029852

Schiffman M, Doorbar J, Wentzensen N, de Sanjosé S, Fakhry C, Monk BJ, et al. (2016). Carcinogenic human papillomavirus infection. *Nat Rev Dis Primers*. 2(1):16086. doi:10.1038/nrdp.2016.86 PMID:27905473

Schiffman M, Herrero R, Desalle R, Hildesheim A, Wacholder S, Rodriguez AC, et al. (2005). The carcinogenicity of human papillomavirus types reflects viral evolution. *Virology*. 337(1):76–84. doi:10.1016/j.virol.2005.04.002 PMID:15914222

Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE (2011). Human papillomavirus testing in the prevention of cervical cancer. *J Natl Cancer Inst*. 103(5):368–83. doi:10.1093/jnci/djq562 PMID:21282563

Sengayi-Muchengeti M, Joko-Fru WY, Miranda-Filho A, Egue M, Akele-Akpo MT, N'da G, et al. (2020). Cervical cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: a population-based registry study. *Int J Cancer*. 147(11):3037–48. doi:10.1002/ijc.33120 PMID:32449157

Shafi MI, Jordan JA, Singer A (2006). The management of cervical intraepithelial neoplasia (squamous). In: Jordan JA, Singer A, editors. The cervix. 2nd ed. Oxford, UK: Blackwell Publishing; pp. 462–77. doi:10.1002/9781444312744.ch31

Simms KT, Steinberg J, Caruana M, Smith MA, Lew JB, Soerjomataram I, et al. (2019). Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020–99: a modelling study. *Lancet Oncol*. 20(3):394–407. doi:10.1016/S1470-2045(18)30836-2 PMID:30795950

Smith HO, Tiffany MF, Qualls CR, Key CR (2000). The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States – a 24-year population-based study. *Gynecol Oncol*. 78(2):97–105. doi:10.1006/gyno.2000.5826 PMID:10926787

Solomon D (1989). The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. Developed and approved at the National Cancer Institute Workshop, Bethesda, Maryland, U.S.A., December 12–13, 1988. *Acta Cytol*. 33(5):567–74. PMID:2781957

Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. (1997). Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet*. 349(9057):978–80. doi:10.1016/S0140-6736(96)08295-5 PMID:9100623

Sripan P, Chitapanarux I, Fidler-Benaoudia MM, Miranda-Filho A, Bardot A, Pongnikorn D, et al. (2019). Impact of universal health care and screening on incidence and survival of Thai women with cervical cancer: a population-based study of the Chiang Mai Province. *Cancer Epidemiol*. 63:101594. doi:10.1016/j.canep.2019.101594 PMID:31539716

Stanley M, Coleman N, Chambers M (1994). The host response to lesions induced by human papillomavirus. *Ciba Found Symp*. 187:21–32, discussion 32–44. PMID:7796671

Stoler MH, Schiffman M; Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group (2001). Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. *JAMA*. 285(11):1500–5. doi:10.1001/jama.285.11.1500 PMID:11255427

Stolnicu S, Barsan I, Hoang L, Patel P, Terinte C, Pesci A, et al. (2018). International Endocervical Adenocarcinoma Criteria and Classification (IECC): a new pathogenetic

classification for invasive adenocarcinomas of the endocervix. *Am J Surg Pathol*. 42(2):214–26. doi:10.1097/PAS.0000000000000986 PMID:29135516

Stolnicu S, Hoang L, Soslow RA (2019). Recent advances in invasive adenocarcinoma of the cervix. *Virchows Arch*. 475(5):537–49. doi:10.1007/s00428-019-02601-0 PMID:31209635

Strander B, Andersson-Ellström A, Milsom I, Sparén P (2007). Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. *BMJ*. 335(7629):1077. doi:10.1136/bmj.39363.471806.BE PMID:17959735

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 71(3):209–49. doi:10.3322/caac.21660 PMID:33538338

Tabbara S, Saleh AD, Andersen WA, Barber SR, Taylor PT, Crum CP (1992). The Bethesda classification for squamous intraepithelial lesions: histologic, cytologic, and viral correlates. *Obstet Gynecol*. 79(3):338–46. doi:10.1097/00006250-199203000-00003 PMID:1738511

Thøgersen H, Møller B, Robsahm TE, Aaserud S, Babigumira R, Larsen IK (2017). Comparison of cancer stage distribution in the immigrant and host populations of Norway, 1990–2014. *Int J Cancer*. 141(1):52–61. doi:10.1002/ijc.30713 PMID:28369751

UNDP (2020). Human development reports. United Nations Development Programme. Available from: http://hdr.undp.org/en/2020-report.

Vaccarella S, Franceschi S, Zaridze D, Poljak M, Veerus P, Plummer M, et al. (2016). Preventable fractions of cervical cancer via effective screening in six Baltic, central, and eastern European countries 2017–40: a population-based study. *Lancet Oncol*. 17(10):1445–52. doi:10.1016/S1470-2045(16)30275-3 PMID:27567054

Vale DB, Sauvaget C, Muwonge R, Thuler LCS, Basu P, Zeferino LC, et al. (2019). Level of human development is associated with cervical cancer stage at diagnosis. *J Obstet Gynaecol*. 39(1):86–90. doi:10.1080/01443615.2018.1463976 PMID:30229689

van der Marel J, van Baars R, Alonso I, del Pino M, van de Sandt M, Lindeman J, et al. (2014). Oncogenic human papillomavirus-infected immature metaplastic cells and cervical neoplasia. *Am J Surg Pathol*. 38(4):470–9. doi:10.1097/PAS.0000000000000174 PMID:24503756

Van Doorslaer K, Burk RD (2010). Evolution of human papillomavirus carcinogenicity. *Adv Virus Res*. 77:41–62. doi:10.1016/B978-0-12-385034-8.00002-8 PMID:20951869

Venetianer R, Clarke MA, van der Marel J, Tota J, Schiffman M, Dunn ST, et al. (2020). Identification of HPV genotypes causing cervical precancer using tissue-based genotyping. *Int J Cancer*. 146(10):2836–44. doi:10.1002/ijc.32919 PMID:32037535

von Knebel Doeberitz M, Prigge ES (2019). Role of DNA methylation in HPV associated lesions. *Papillomavirus Res*. 7:180–3. doi:10.1016/j.pvr.2019.03.005 PMID:30978415

Wada T, Ohishi Y, Kaku T, Aman M, Imamura H, Yasutake N, et al. (2017). Endocervical adenocarcinoma with morphologic features of both usual and gastric types: clinicopathologic and immunohistochemical analyses and high-risk HPV detection by in situ hybridization. *Am J Surg Pathol*. 41(5):696–705. doi:10.1097/PAS.0000000000000833 PMID:28296678

Wang SS, Sherman ME, Hildesheim A, Lacey JV Jr, Devesa S (2004). Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. *Cancer*. 100(5):1035–44. doi:10.1002/cncr.20064 PMID:14983500

Wassie M, Argaw Z, Tsige Y, Abebe M, Kisa S (2019). Survival status and associated factors of death among cervical cancer patients attending at Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia: a retrospective cohort study. *BMC Cancer*. 19(1):1221. doi:10.1186/s12885-019-6447-x PMID:31842805

Wentzensen N, Bergeron C, Cas F, Vinokurova S, von Knebel Doeberitz M (2007). Triage of women with ASCUS and LSIL cytology: use of qualitative assessment of p16[INK4a] positive cells to identify patients with high-grade cervical intraepithelial neoplasia. *Cancer*. 111(1):58–66. doi:10.1002/cncr.22420 PMID:17186505

Wentzensen N, Clarke MA, Bremer R, Poitras N, Tokugawa D, Goldhoff PE, et al. (2019). Clinical evaluation of human papillomavirus screening with p16/Ki-67 dual stain triage in a large organized cervical cancer screening program. *JAMA Intern Med*. 179(7):881–8. doi:10.1001/jamainternmed.2019.0306 PMID:31081870

Wentzensen N, Schiffman M, Dunn T, Zuna RE, Gold MA, Allen RA, et al. (2009). Multiple human papillomavirus genotype infections in cervical cancer progression in the study to understand cervical cancer early endpoints and determinants. *Int J Cancer*. 125(9):2151–8. doi:10.1002/ijc.24528 PMID:19585494

WHO (2014). Comprehensive cervical cancer control. A guide to essential practice. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/.

WHO (2019). WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/329299.

WHO (2020). WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer. Geneva, Switzerland: World Health

Organization. Available from: https://apps.who.int/iris/handle/10665/331698.

WHO Classification of Tumours Editorial Board (2020). Female genital tumours. 5th ed. Lyon, France: International Agency for Research on Cancer (WHO Classification of Tumours series, Vol. 4). Available from: https://publications.iarc.fr/592.

Yagi A, Ueda Y, Kakuda M, Tanaka Y, Ikeda S, Matsuzaki S, et al. (2019). Epidemiologic and clinical analysis of cervical cancer using data from the population-based Osaka Cancer Registry. *Cancer Res.* 79(6):1252–9. doi:10.1158/0008-5472.CAN-18-3109 PMID:30635276

Zahreddine M, Mayrand MH, Therrien C, Trevisan A, Dagenais C, Monnier P, et al. (2020). Antibodies to human papillomavirus types 6, 11, 16 and 18: vertical transmission and clearance in children up to two years of age. *EClinicalMedicine.* 21:100334. doi:10.1016/j.eclinm.2020.100334 PMID:32382718

2. CERVICAL CANCER SCREENING PROGRAMMES

2.1 Introduction

The purpose of cervical cancer screening and treatment is to reduce the incidence of and mortality from cervical cancer by identifying women with precancerous cervical lesions and early invasive cancer and treating them appropriately.

Broadly, there are two main categories of screening: (i) organized population-based programmes and (ii) opportunistic screening and non-population-based screening; the latter may be conducted within the framework of screening programmes that have different levels and methods of coordination and organization (Basu et al., 2019).

A screening programme provides a detailed pathway that starts by identifying the people who are eligible for screening and ends by reporting the programme outcomes. This pathway includes the following steps: invitation and information, administration of the screening test or tests, communication of the screening test results, management of women with a positive screening test result, and provision of treatment and care of detected precancers and cancers. Adherence to and high quality of the entire screening and management pathway are central to the effectiveness of a screening programme; measures should be in place to ensure high participation of the target population, high quality of the primary screening test, effective follow-up of women with positive screening test results, and appropriate subsequent treatment and care (IARC, 2005).

An organized screening programme is defined as one that has "an explicit policy with specified age categories, method, and interval for screening; a defined target population; a management team responsible for implementation; a health-care team for decisions and care; a quality-assurance structure; and a method for identifying cancer occurrence in the target population" (IARC, 2005). An organized population-based programme is further defined as an organized programme that has a mechanism to identify the eligible individuals and send personal invitations to the eligible individuals to attend screening (Basu et al., 2019). It involves a higher degree of programme management and requires quality control of all steps of the screening and management pathway: planning and implementation, coordination of the delivery of services, invitation and recall, administration of the screening test, further assessment and follow-up of women with a positive screening test result, and performance monitoring and evaluation, which involve the development of standardized indicators (Arbyn et al., 2010; Vale et al., 2019a; see also Section 2.3).

In contrast, in opportunistic screening, women are screened because they have asked

to be screened or have been offered the test by a health professional in the context of the patient–practitioner relationship. Opportunistic screening is often characterized by high participation in selected parts of the population, which are screened too frequently, combined with low participation in other population groups with lower socioeconomic status, and heterogeneous quality (Arbyn et al., 2010). Studies indicate that organized population-based screening programmes are more effective, more cost-effective, and more equitable than opportunistic screening (Arbyn et al., 2009; Palència et al., 2010). They also offer greater protection against the harmful effects associated with poor-quality screening or screening that is carried out too frequently (Miles et al., 2004).

In practice, cervical cancer screening is performed in many ways, and perceptions of what constitutes a screening programme vary widely; differentiation between organized and unorganized screening programmes is, to a certain extent, arbitrary and does not take into account the continuous gradient from poorly organized to highly organized programmes (von Karsa et al., 2008). Furthermore, characterization of a screening programme or screening activity is sometimes not reported properly, which hinders comparison between countries. The description of the availability of cervical cancer screening programmes and activities in the different countries in this section relies mostly on the available publications and may not always reflect the reality. The existence of a programme does not necessarily mean that it is covered by a health insurance programme and accessible to all. In most countries, screening is still opportunistic. The lack of adequate individualized data sources that can be used to identify eligible individuals to be invited (Vale et al., 2019a), the difficulty of ensuring appropriate follow-up after a positive screening test result, and the limited access to treatment and care are major practical and ethical issues for the implementation of cervical

cancer screening in low- and middle-income countries (LMICs).

The screening tests currently used in existing programmes globally include human papillomavirus (HPV) testing alone, HPV and cytology co-testing, cytology, and visual inspection.

2.2 Availability and use of cervical cancer screening worldwide

The countries included in each WHO region are listed in the Glossary.

2.2.1 WHO African Region

In low-resource settings such as some African countries, screening programmes are very difficult to implement and WHO recommends a method based on a screen-and-treat approach, in which the treatment decision is based on the result of a screening test and treatment of precancerous lesions is initiated immediately after a positive screening test result (WHO, 2013; see Section 5.1).

Several African countries are in the early stages of exploring and developing tailored strategies in cervical cancer prevention and control. Sustainable programmes are usually lacking because of poor medical infrastructures and funding. In the WHO African Region, most countries have started to implement national guidelines and recommendations (Table 2.1). Most follow the WHO screen-and-treat guidelines and use visual inspection with acetic acid (VIA) with cryotherapy, whereas others continue to use cytology-based screening or are exploring HPV testing (Sahasrabuddhe et al., 2012; Oluwole & Kraemer, 2013; Makura et al., 2016). With the exception of South Africa, which has had an organized population-based programme since 2003, most countries in Africa have no organized cervical cancer screening (Table 2.1). Several countries, such as Algeria, Cameroon, and

Table 2.1 Policies and practice for cervical cancer screening in countries of the WHO African Region

Country[a]	Type of programme or setting	Start year or period	Screening method	Target age range (years)	Interval (years)	Target age range for HIV+ women (years)	Interval for HIV+ women (years)	References
Algeria	Non-population-based	1997	Cytology	30–60	3	–	–	Sancho-Garnier et al. (2013); République Algérienne Démocratique et Populaire (2014); Giordano et al. (2016)
Angola	Pilot project	2002–2006	VIA/VILI	25–59	–	–	–	Muwonge et al. (2010)
Benin	Opportunistic	–	Cytology	–	–	–	–	Bruni et al. (2019a)
Botswana	Pilot project	2009–2011	VIA	30–49	–	–	–	Grover et al. (2015); Johnson et al. (2020)
	Scaling up	2014	VIA	30–49	5	–	3	
Burkina Faso	Pilot project	2010–2014	VIA	25–59	3	–	1	Sawadogo et al. (2014); Ouedraogo et al. (2018); WHO (2020e)
Cameroon	Non-population-based	2007	VIA/VILI	> 25	3–5	> 21	–	DeGregorio et al. (2017)
	Pilot project	2015	HPV self-sampling + VIA/VILI	30–49	5 for HPV– women	_	–	Kunckler et al. (2017)
Congo	Pilot project	1999–2003	VIA/VILI	25–65	–	–	–	Muwonge et al. (2007)
Côte d'Ivoire	Pilot project	2009–2012	VIA	30–50	3–5	–	1	Anderson et al. (2015); Bruni et al. (2019a); Sengayi-Muchengeti et al. (2020)
Eswatini	Pilot project	2010	VIA or cytology	25–45	2	–		Jolly et al. (2017)
Ethiopia	Pilot project	2010–2014	VIA	NS	30–45		1	Shiferaw et al. (2016); WHO (2020f)
Gabon	Non-population-based	2014	VIA	> 25	3	–	–	Fondation Sylvia Bongo Ondimba, Ministère de la Santé gabonais (2014); Assoumou et al. (2015)
Gambia	Pilot project	–	VIA	–	–	–	–	Bruni et al. (2019a)
Ghana	Pilot project	2005	VIA	25–45	3–5	–	–	Ministry of Health Ghana (2011)
			Cytology	> 45	–	–	–	
Guinea	Pilot project	2003–2005	VIA	–	–	–	–	Bruni et al. (2019a)
Kenya	Non-population-based	2013	VIA	25–49	5	18–65	1	Ministry of Public Health and Sanitation Kenya, Ministry of Medical Services Kenya (2012); Khozaim et al. (2014); Sengayi-Muchengeti et al. (2020)
			Cytology	> 50	5			

Table 2.1 (continued)

Country[a]	Type of programme or setting	Start year or period	Screening method	Target age range (years)	Interval (years)	Target age range for HIV+ women (years)	Interval for HIV+ women (years)	References
Lesotho	Unknown	–	VIA	–	–	–	–	Bruni et al. (2019a)
Madagascar	Non-population-based	2007	VIA or cytology	25–49	3	–	–	Ministère de la Santé Publique Madagascar (2011); Broquet et al. (2015); République de Madagascar, OMS (2016); Benski et al. (2019); Dumont et al. (2019)
Malawi	Non-population-based	2004	VIA	25–50 21–25 (sexually active women)	3	All HIV+ women	2	Maseko et al. (2014); Maseko et al. (2015); Msyamboza et al. (2016); Ministry of Health Malawi (2018); Bruni et al. (2019a); Malawi Ministry of Health and Population (2019)
			Cytology or HPV test	50–65 (never screened)	One screen	–		
Mali	Pilot project	1999–2003	VIA/VILI	25–65	3–5	–	–	Muwonge et al. (2007); Bruni et al. (2019a)
Mauritius	Pilot project	2003	VIA	35–55	5			Bruni et al. (2019a); Sengayi-Muchengeti et al. (2020)
Mozambique	Non-population-based	2009	VIA	30–55	1	–		Moon et al. (2012); Brandão et al. (2019)
Namibia	Pilot project	NA	VIA or cytology	21–64	1	–	–	Bruni et al. (2019a); Sengayi-Muchengeti et al. (2020)
Niger	Pilot project	1999–2003	VIA/VILI	25–65		–	–	Muwonge et al. (2007)
Nigeria	Pilot project	2011–2014	VIA	30–50	3–5	–	–	Anorlu et al. (2003); Adepoju et al. (2016); Chigbu et al. (2017)
Rwanda	Non-population-based	2013	HPV test + VIA	35–45	7 (HPV– women) 3 (HPV+ women)	30–50	1	Binagwaho et al. (2013)
Senegal	Pilot project	2016	VIA or cytology	20–64	2	–	–	Gabrielli et al. (2018)
Seychelles	Non-population-based	2013–2014	Cytology	Sexually active women	2	–	–	Bovet et al. (2013); Bruni et al. (2019a)

Table 2.1 (continued)

Country[a]	Type of programme or setting	Start year or period	Screening method	Target age range (years)	Interval (years)	Target age range for HIV+ women (years)	Interval for HIV+ women (years)	References
South Africa	Population-based	2003	Cytology	30–50	10	–	3	Bruni et al. (2019a); National Department of Health South Africa (2020); WHO (2020g)
Togo	Pilot project		VIA or cytology	35–65		–	–	Bruni et al. (2019a)
Uganda	Opportunistic	–	VIA	–	–	–	–	Paul et al. (2013); Kumakech et al. (2014); Ndejjo et al. (2017)
United Republic of Tanzania	Pilot project	2009–2012	VIA	30–50	3–5	–	1	Kahesa et al. (2012); Plotkin et al. (2014); Anderson et al. (2015); Masalu et al. (2017); Tsu et al. (2018)
Zambia	Non-population-based	2006	VIA	30–50	5	25–59	3	Mwanahamuntu et al. (2009, 2011); Ministry of Community Development, Mother and Child Health Zambia, Ministry of Health Zambia (2015); Bruni et al. (2019a)
Zimbabwe	Pilot project	2002–2003	VIA	25–59	3	–	–	Bruni et al. (2019a); Sengayi-Muchengeti et al. (2020)

HPV, human papillomavirus; NS, not specified; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

[a] Burundi, Cabo Verde, Chad, Comoros, Eritrea, Guinea-Bissau, Liberia, Mauritania, Sao Tome and Principe, and Sierra Leone have no programme (Bruni et al., 2019a).

Zambia, have implemented national non-population-based screening programmes.

In Algeria, the national cervical cancer screening programme has been based on cytology since 1997. It was revamped in 2015–2020, taking into account organizational and financial aspects, including plans to evaluate the programme, additional training for staff involved in cytology screening, and the introduction of HPV triage. Currently, the Pap test is offered for women aged 30–60 years and repeated every 3 years (Sancho-Garnier et al., 2013; République Algérienne Démocratique et Populaire, 2014; Giordano et al., 2016).

The Zambian Ministry of Health has integrated a cervical cancer screening programme, called the Cervical Cancer Prevention Program in Zambia (CCPPZ), into the existing infrastructure dedicated to HIV/AIDS care. Since the launch of the programme in 2006, women have been screened, regardless of their HIV status, by the VIA test and then treated immediately with cryotherapy after a positive screening test result, according to the screen-and-treat approach (Mwanahamuntu et al., 2009, 2011). The CCPPZ is the largest screen-and-treat programme in Africa (DeGregorio et al., 2017).

Cameroon's largest cervical cancer screening programme, called the Women's Health Program, was founded in 2007 by Cameroon Baptist Convention Health Services and integrated into an existing HIV/AIDS care system, modelled on the CCPPZ. The screening programme is based on the screen-and-treat approach and targets women aged > 25 years (> 21 years for HIV-positive women). It uses the VIA screening test coupled with same-day cryotherapy treatment for women with a positive screening test result (DeGregorio et al., 2017).

A few other countries have also implemented national non-population-based programmes, but many countries still rely on pilot projects (Table 2.1). In the past decade, several large initiatives have been set up through public–private partnerships. These initiatives, such as the Pink Ribbon Red Ribbon campaign, which was launched in September 2011, and Go Further, which was launched in 2018, invest in partner countries to integrate and scale up cervical cancer screening and treatment services within existing platforms for HIV/AIDS care and women's health (Sahasrabuddhe et al., 2012; Oluwole & Kraemer, 2013; George W. Bush Presidential Center, 2017; Go Further, 2019; 2020a, b, c).

Scale-up of cervical cancer screening remains challenging; very few countries have achieved nationwide coverage of their target population and this has been difficult to measure. Most countries in the WHO African Region rely on self-reported surveys such as the STEPwise approach to Surveillance (STEPS) method (WHO, 2020a), Demographic and Health Surveys, or Facility Surveys to assess their coverage. For example, Benin conducted a survey in 2015 and reported that only 0.9% of women aged 30–44 years had been screened for cervical cancer (WHO, 2020a), whereas Botswana reported in 2015 that about 50.6% of women aged 30–44 years had been screened (WHO, 2020a). Within its organized programme, South Africa determined that in 2013–2014 the median Pap test coverage was 33% overall and 31% in HIV-positive women across the country's 52 districts. Most districts had coverage below 50%, and very few districts (3 of 52) reached the target of > 70% coverage (Makura et al., 2016).

2.2.2 WHO Eastern Mediterranean Region

In the WHO Eastern Mediterranean Region, most countries practise opportunistic screening based on cytology; still, a few have implemented non-population-based screening programmes within a national cancer control plan. No countries have an active invitation mechanism for screening; women are typically offered cervical cancer screening when they visit a primary health-care unit or their gynaecologist. Because

of this, the participation rates remain low (Table 2.2).

(a) North Africa (Djibouti, Egypt, Libya, Morocco, Somalia, Sudan, and Tunisia)

In 2010, Morocco initiated a non-population-based screening programme for women aged 30–49 years as part of the National Plan for Prevention and Control of Cancer. By 2017, the programme had been implemented in eight of the 12 regions in Morocco. This programme was integrated with primary health care in the public sector and used the VIA screening test, which was offered every 3 years. In 2015, coverage of the target population was measured to be low (30.8%). In the private sector, screening using cytology is provided, but no valid data are available (Giordano et al., 2016; CIRC, Ministère de la Santé, Fondation Lalla Salma, 2017; Bruni et al., 2019a; Selmouni et al., 2019).

In Tunisia, a non-population-based screening programme based on cytology has been implemented and offers screening every 5 years to women aged 35–65 years in primary care centres, hospitals, and family planning clinics (Sancho-Garnier et al., 2013; Ministère de la Santé Tunisien, 2015; Giordano et al., 2016; Bruni et al., 2019a). Coverage has been reported to be consistently very low between 2003 and 2015 (14%) because of a lack of human resources, poor awareness of cancer risk in the population, and challenges related to quality control and achieving timely follow-up (Sancho-Garnier et al., 2013; Ministère de la Santé Tunisien, 2015). Opportunistic Pap testing in the private sector is available, but it is not supported by the national health insurance system and no data are available (Sancho-Garnier et al., 2013; Giordano et al., 2016).

In Egypt, opportunistic screening using Pap testing is offered to women aged 20–50 years who attend health-care facilities on an in- and outpatient basis for other gynaecological problems, primarily through universities and teaching hospitals (Sancho-Garnier et al., 2013; Giordano et al., 2016; Bruni et al., 2019a).

No cervical cancer screening programmes are in place in the other North African countries (i.e. Djibouti, Libya, Somalia, and Sudan) (Bruni et al., 2019a).

(b) Gulf countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates) and Yemen

None of the Gulf countries have an organized nationwide screening programme for cervical cancer (Sancho-Garnier et al., 2013; Al-Othman et al., 2015). Opportunistic screening using Pap testing is available in the public and private sector (generally free of charge in the public sector). In Yemen, there is no organized national screening programme and cytology-based screening is available in the private sector only. Target populations include women aged 20–69 years in Oman, 30–64 years in the United Arab Emirates, and 35–64 years in Bahrain (and were not specified in other countries). In Saudi Arabia and Kuwait, target populations for cervical cancer screening include married women only. Screening coverage varies, ranging from 5–17% in Saudi Arabia (as reported in 2009) to about 70% in Oman (as reported in 2012) (Sancho-Garnier et al., 2013).

(c) Other countries (Afghanistan, Islamic Republic of Iran, Jordan, Lebanon, Pakistan, West Bank and Gaza Strip, and Syrian Arab Republic)

The Syrian Arab Republic has a non-population-based screening programme based on cytology for women aged 15–55 years (Giordano et al., 2016; Bruni et al., 2019b; WHO, 2020b). In Jordan and Lebanon, opportunistic screening is performed in the public and private sector using cytology, and both countries organize nationwide calls inviting women to cervical cancer screening (Sancho-Garnier et al., 2013; Giordano et al., 2016; Sharkas et al., 2017; Bruni et al., 2019b). Between 2002 and 2010, population coverage was

Table 2.2 Policies and practice for cervical cancer screening in countries of the WHO Eastern Mediterranean Region

Country or territory[a]	Type of programme or setting	Start year	Screening method	Target age range (years)	Interval (years)	References
Afghanistan	Opportunistic	–	VIA or cytology	15–49	5	Bruni et al. (2019b)
Bahrain	Opportunistic	–	Cytology	35–64	3–5	Sancho-Garnier et al. (2013); Al-Othman et al. (2015)
Egypt	Opportunistic	–	Cytology	20–50	–	Giordano et al. (2016)
Iran (Islamic Republic of)	Opportunistic	–	Cytology	35–54 (married women)	3 yr after 3 consecutive annual negative tests	Farshbaf-Khalili et al. (2015); Aminisani et al. (2016); Khazaee-Pool et al. (2018); Refaei et al. (2018); Bruni et al. (2019b)
Jordan	Opportunistic	–	Cytology	25–35	–	Bruni et al. (2019b)
Kuwait	Opportunistic	–	Cytology	Married women	5	Al Sairafi & Mohamed (2009); Sancho-Garnier et al. (2013); Al-Othman et al. (2015)
Lebanon	Opportunistic	–	Cytology	3 yr after becoming sexually active	2–3	Sancho-Garnier et al. (2013)
Morocco	Non-population-based	2010	VIA or cytology	30–49	3	Sancho-Garnier et al. (2013); Giordano et al. (2016); CIRC, Ministère de la Santé, Fondation Lalla Salma (2017); Selmouni et al. (2019)
Oman	Opportunistic	–	Cytology	20–69	3	Sancho-Garnier et al. (2013); Al-Othman et al. (2015)
Pakistan	Opportunistic	–	VIA	30–60	5	Bruni et al. (2019b)
Qatar	Opportunistic	–	Cytology	21–65	1	Al-Meer et al. (2011); Sancho-Garnier et al. (2013); Al-Othman et al. (2015)
Saudi Arabia	Opportunistic	–	Cytology	21–65 (married women)	3	Sait (2009); Sancho-Garnier et al. (2013); Al-Othman et al. (2015); Bruni et al. (2019b)
Syrian Arab Republic	Non-population-based	–	Cytology	15–55	–	Bruni et al. (2019b); WHO (2020b)
Tunisia	Non-population-based	1990	Cytology	35–59	5	Sethom et al. (1989); Ben Aissa et al. (2002); Sancho-Garnier et al. (2013); Ministère de la Santé Tunisien (2015); WHO (2020i)

Table 2.2 (continued)

Country or territory[a]	Type of programme or setting	Start year	Screening method	Target age range (years)	Interval (years)	References
United Arab Emirates	Opportunistic	–	Cytology	30–64	3	Sancho-Garnier et al. (2013); Al-Othman et al. (2015); Badrinath et al. (2004)
Yemen	Opportunistic	–	Cytology	–	–	Sancho-Garnier et al. (2013); Al-Othman et al. (2015)

VIA, visual inspection with acetic acid; yr, year or years.

[a] Djibouti, Libya, Somalia, Sudan, and West Bank and Gaza Strip have no programme (Halahleh & Gale, 2018; Bruni et al., 2019a, b; WHO, 2020h).

reported to be about 25% in Lebanon (Sancho-Garnier et al., 2013); these data are not available for Jordan.

In the Islamic Republic of Iran, opportunistic screening is based on cytology, targeting married women aged 35–54 years. Although robust national coverage estimates are not available, regional estimates from 2014 suggest coverage rates of about 30–50% among eligible women (Farshbaf-Khalili et al., 2015; Aminisani et al., 2016).

There is opportunistic screening in Pakistan based on VIA (Bruni et al., 2019b). There is no cervical cancer screening activity for the other countries in the region.

2.2.3 WHO European Region

In Europe, the first organized cervical cancer screening programmes were initiated in the late 1950s and early 1960s: 1959 in Østfold county, Norway; 1960 in Grampian region, Scotland; 1962 in Frederiksberg municipality, Denmark (Macgregor et al., 1985; Magnus et al., 1987; Bigaard et al., 2000). In the following years, screening based on the Pap test was introduced in most European countries, either in organized population-based programmes or as an opportunistic activity initiated by individual women or their physicians (Ronco & Anttila, 2009).

Information about cervical cancer screening policies, strategies, implementation status, coverage, and participation is available from several recent reviews and surveys (von Karsa et al., 2008; Elfström et al., 2015; Ponti et al., 2017; Basu et al., 2018; Vale et al., 2019b; see also Section 2.3).

(a)   Policies and guidelines

The first European guidelines for quality assurance in cervical cancer screening were published in 1993, as part of the Europe Against Cancer programme; they outlined the principles of organized population-based screening (Coleman et al., 1993). In 2003, the European Union (EU) Council recommended the implementation of organized screening programmes with quality assurance processes (Ronco & Anttila, 2009). The second edition of the European guidelines for quality assurance in cervical cancer screening was published in 2008, with considerable attention given to organized population-based programme policies that maximize the health benefits of screening and minimize the harms (Arbyn et al., 2010; see also Section 2.3.2). Specifically, the guidelines recommended cytology screening at 3- to 5-year intervals when test results are normal, generally starting at age 20–30 years (but preferentially not before age 25 or 30 years) and ending at age 60–65 years. The guidelines were updated in 2015 to incorporate advances in screening technologies and prevention strategies (von Karsa et al., 2015). The updated guidelines recommend primary testing for HPV at an interval of at least 5 years starting at age 30–35 years (von Karsa et al., 2015). They also recommend against co-testing (i.e. HPV and cytology primary testing) at any age.

(b)   Implementation

(i)   Type of programme and implementation status

In the EU, progress in the implementation of the EU Council recommendations on cancer screening was first assessed in a report published in 2008 (von Karsa et al., 2008) and subsequently in a second report published in 2017 (updated to July 2016) (Ponti et al., 2017). The findings of the second report showed that the approach to cervical cancer screening has been variable across the EU Member States, with many improvements in the implementation of population-based screening since the previous report. For instance, by July 2016, 22 EU Member States (which included the United Kingdom at that time) had implemented, piloted,

or planned population-based cervical cancer screening programmes (Table 2.3), compared with only 17 countries in 2007 (Ponti et al., 2017; Basu et al., 2018). All 22 Member States with population-based programmes had documented policies on cervical screening, although such policies were mandated by law in only six of them. Nationwide rollout of population-based cervical cancer screening was complete in 10 countries (Denmark, Estonia, Finland, Lithuania, the Netherlands, Poland, Portugal, Slovenia, Sweden, and the United Kingdom), partial in nine countries (Belgium, Croatia, Czechia, France, Hungary, Ireland, Italy, Latvia, and Romania), planned in two countries (Germany and Slovakia), and in the pilot phase in one country (Malta) (Basu et al., 2018; Vale et al., 2019b). Among age-eligible women in the EU, 72.3% were residents of Member States that had implemented or planned population-based screening for cervical cancer in 2016, compared with 51.3% in 2007 (Basu et al., 2018). All EU Member States with population-based cervical cancer screening programmes, except Lithuania, have a team responsible for programme implementation (no information was provided for Croatia) (Basu et al., 2018). All programmes are publicly funded, with screening tests provided free of charge (except in Croatia). Screening registries exist in all population-based programmes (except in Lithuania).

In non-EU countries in Europe, some organized population-based programmes were implemented nationwide as early as the 1960s (Iceland) and 1990s (Norway) and as recently as 2004 (Turkey) and 2011 (North Macedonia) (Davies & Dimitrievska, 2015; Gultekin et al., 2018; Gultekin et al., 2019; Partanen et al., 2019; Table 2.3).

In the countries of the former Soviet Union (with the exception of the Baltic States, which are part of the EU), cervical cancer screening is mostly opportunistic and uses cytology based on Romanowsky–Giemsa staining (see Section 4.3.4; Rogovskaya et al., 2013; Altobelli et al., 2019; Aimagambetova et al., 2021). In most countries, screening is paid for by the government and is available to residents free of charge. Although the screening programmes in most countries do have some organized features, these programmes are not population-based, because they lack widespread call–recall systems, have low coverage, and do not have quality assurance systems with centralized screening registries (Rogovskaya et al., 2013). In the Russian Federation, Moscow was the first region to implement a cervical cancer screening programme with call–recall system elements in 2002, followed by similar efforts in selected regions on an irregular basis. In the Caucasus region, Armenia and Georgia have cytology-based cervical cancer screening programmes; coverage rates are very low. Although Pap testing is performed at different levels of the health-care system in Azerbaijan, it is not widely accessible and no national screening programme exists (Rogovskaya et al., 2013). In all the Central Asian countries, cytology-based cervical cancer screening is currently available (Aimagambetova et al., 2021). However, screening is mainly opportunistic, with no active invitation process, and coverage has been low or unreported.

(ii) Screening method

Cytology, which has been the cornerstone of cervical cancer prevention for decades, remains the screening test used in most European countries. However, HPV testing is being gradually introduced as the primary screening test. By July 2016, primary HPV screening had already been introduced in some regions in several EU Member States as a stand-alone test followed by triage with cytology (Denmark, Finland, Italy, and Sweden), as co-testing combined with cytology (Romania and Malta), and both as a stand-alone test and as co-testing (Portugal) (Ponti et al., 2017; Basu et al., 2018).

Table 2.3 Policies and practice for cervical cancer screening in countries of the WHO European Region

Country or region	Type of programme	Start year	Target age range (years)	Primary screening method (age group)	Triage test[a]	Interval (age group) (years)	Invitation coverage (%)[b] (year)	Examination coverage (%) (year)	Participation rate (%) (year)	References
Albania	Opportunistic	NR	> 20	Cytology		2–3		2.7 (2002)		Altobelli et al. (2019)
Andorra	Opportunistic	NR	> 18	Cytology		1		61.4 (2011)		Altobelli et al. (2019)
Armenia	Non-population-based	NR	30–60	Cytology		3		9.3 (2010)		Altobelli et al. (2019)
Austria	Opportunistic	1970	> 18	Cytology		1		86.6 (2014)		Ponti et al. (2017); Altobelli et al. (2019)
Azerbaijan	None		NR	VIA				1.1 (2001)		Altobelli et al. (2019)
Belarus	Opportunistic	NR	> 18	Cytology		1		75 (2015)		Altobelli et al. (2019)
Belgium (Flanders)[c]	Population-based	2013	25–64	Cytology	HPV test	3	58.9 (2013)	41.3 (2013)	11.4 (2013)	Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Vale et al. (2019b)
Bosnia and Herzegovina	Opportunistic	NR	21–70	Cytology		1		39.8 (2003)		Altobelli et al. (2019)
Bulgaria	Opportunistic	NR	30–59	Cytology		3		46.8 (2008)		Altobelli et al. (2019)
Croatia	Population-based	2012	25–64	Cytology	HPV test	3			10.3 (2013)	Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Vale et al. (2019b)
Cyprus	Opportunistic	NR	24–65	Cytology		NR		67.4 (2012)		Altobelli et al. (2019)
Czechia	Population-based	2008	≥ 15	Cytology	HPV test	1		49.3 (2013)		Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Vale et al. (2019b)
Denmark	Population-based	2006	23–64	Cytology (23–29) HPV test and cytology (30–59)[d] HPV test (60–64)	HPV test	3 (23–49) 5 (50–64)	67.1 (2013)	82.1 (2013)	64.4 (2013)	Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Partanen et al. (2019); Vale et al. (2019b)

Table 2.3 (continued)

Country or region	Type of programme	Start year	Target age range (years)	Primary screening method (age group)	Triage test[a]	Interval (age group) (years)	Invitation coverage (%)[b] (year)	Examination coverage (%) (year)	Participation rate (%) (year)	References
Estonia	Population-based	2006	30–59	Cytology	HPV test or repeat cytology at 12 months	5	77.1 (2014)	44.4 (2013)	57.5 (2013)	Ponti et al. (2017); Basu et al. (2018); Partanen et al. (2019); Vale et al. (2019b)
Finland	Population-based	1963	30–64[e]	HPV test or cytology[f]	Cytology or HPV test[g]	5	97.9 (2012)	66.0 (2013)	67.4 (2013)	Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Partanen et al. (2019); Vale et al. (2019b); Maver & Poljak (2020)
France[h]	Population-based	1991	25–65	Cytology (25–29) HPV test (30–65)	HPV test Cytology	3[i] (25–29), cytology 5 (30–65), HPV test	56.0 (2012)	64.8 (2013)	21.1 (2013)	Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Vale et al. (2019b); French Government (2020)
Georgia	Non-population-based	NR	25–60	Cytology		3		9.0 (2011)		Altobelli et al. (2019)
Germany[j]	Opportunistic; population-based planned	1971	≥ 20	Cytology		1				Basu et al. (2018); Chrysostomou et al. (2018)
Greece	Opportunistic	1991	≥ 20	Cytology		1		75.5 (2014)		Altobelli et al. (2019)
Hungary	Population-based	2003	25–65	Cytology		3	15.2 (2013)	50.6 (2013)	29.6 (2013)	Ponti et al. (2017); Basu et al. (2018); Vale et al. (2019b)
Iceland	Population-based	1964	23–65	Cytology	HPV test	3				Sigurdsson (2010); Partanen et al. (2019)
Ireland	Population-based	2008	25–65	HPV test		3 (25–29) 5 (30–65)		80.2 (2013)		Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Vale et al. (2019b); HSE (2020)
Israel	Opportunistic		25–65	Cytology		3		32.0 (2008)		Altobelli et al. (2019)
Italy	Population-based	1989	25–64	Cytology (25–30) HPV test (30–64)	HPV test[k] Cytology or HPV16/18 genotyping[l]	3 (25–30), cytology 5 (30–64), HPV test	65.1 (2013)	30.6 (2013)	41.5 (2013)	Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Vale et al. (2019b); Maver & Poljak (2020)
Kazakhstan	Opportunistic	2006	18–49	Cytology		4		45.9 (2016)		Aimagambetova et al. (2021)

Table 2.3   (continued)

Country or region	Type of programme	Start year	Target age range (years)	Primary screening method (age group)	Triage test[a]	Interval (age group) (years)	Invitation coverage (%)[b] (year)	Examination coverage (%) (year)	Participation rate (%) (year)	References
Kyrgyzstan	Opportunistic	2013	NR	Cytology		5		10–50 (2015)		Altobelli et al. (2019); Aimagambetova et al. (2021)
Latvia	Population-based	2009	25–69	Cytology		3	92.7 (2013)	26.0 (2013)	35.1 (2013)	Ponti et al. (2017); Basu et al. (2018)
Lithuania	Population-based	2004	25–59	Cytology		3	75.5 (2013)	48.3 (2013)	47.9 (2013)	Ponti et al. (2017); Basu et al. (2018)
Luxembourg	Opportunistic	1990	> 15	Cytology		1				Ponti et al. (2017); Altobelli et al. (2019)
Malta[m]	Population-based	2015	25–35	Cytology and HPV test		3				Basu et al. (2018)
Monaco	Opportunistic	NR	21–65	Cytology		1				Altobelli et al. (2019)
Montenegro	Opportunistic	NR	25–64	Cytology		3				Altobelli et al. (2019)
Netherlands	Population-based	1970	30–60[n]	HPV test	Cytology	5 (30–40) 10 (≥ 40)	96.7 (2013)		66.3 (2013)	Ponti et al. (2017); Basu et al. (2018); Maver & Poljak (2020)
North Macedonia[o]	Population-based	2011	30–55 (24–60)[p]	Cytology		3				Poljak et al. (2013); Davies & Dimitrievska (2015); Altobelli et al. (2019)
Norway	Population-based	1992	25–69	Cytology (25–33) HPV test (34–69)	HPV test or cytology	3 (25–33) 5 (34–69)				Partanen et al. (2019)
Poland	Population-based	2006	25–59	Cytology (25–29) Cytology and HPV test (30–59)	HPV test	3	97.7 (2013)	21.1 (2013)	18.2 (2013)	Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018)
Portugal	Population-based	1990	25– < 60	Cytology and HPV test		3	18.6 (2013)	23.9 (2013)		Ponti et al. (2017); Basu et al. (2018); Vale et al. (2019b); Ministério da Saúde de Portugal (2021)
Republic of Moldova	Opportunistic	NR	> 20	Cytology		2		70.0 (2015)		Rogovskaya et al. (2013); Altobelli et al. (2019)

Table 2.3   (continued)

Country or region	Type of programme	Start year	Target age range (years)	Primary screening method (age group)	Triage test[a]	Interval (age group) (years)	Invitation coverage (%)[b] (year)	Examination coverage (%) (year)	Participation rate (%) (year)	References
Romania[q]	Population-based	2012	25–64	Cytology and HPV test		5	65.0 (2013)	9.2 (2013)	14.2 (2013)	Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018); Vale et al. (2019b)
Russian Federation	Non-population-based	2002	> 18	Cytology		1		72.0 (2012)		Rogovskaya et al. (2013); Altobelli et al. (2019)
San Marino	Population-based	2006	25–65	Cytology (20–30) HPV test (30–65)		3 (25–30), cytology 5 (30–65), HPV test		82.0 (2017)		Altobelli et al. (2019)
Serbia	Population-based	2008	25–65	Cytology		3		57.1 (2013)		Poljak et al. (2013); Altobelli et al. (2019)
Slovakia	Population-based, planned	2008	23–64	Cytology	HPV test	3[l]				Basu et al. (2018); Chrysostomou et al. (2018)
Slovenia	Population-based	2003	20–64	Cytology	HPV test	3[l]		77.4 (2013)		Ponti et al. (2017); Basu et al. (2018); Chrysostomou et al. (2018)
Spain	Opportunistic	NR	25–65	Cytology (25–65) HPV test (30–65)		3, cytology 5, HPV test		72.7 (2014)		Ponti et al. (2017); Altobelli et al. (2019)
Sweden	Population-based	1967	23–64	Cytology (23–29) HPV test (30–64)	HPV test Cytology	3 (23–49) 7 (50–64)	80.7 (2013)	86.3 (2013)	52.7 (2013)	Ponti et al. (2017); Basu et al. (2018); Maver & Poljak (2020); Partanen et al. (2019)
Switzerland	Opportunistic	Late 1960s	> 20	Cytology		3		74.5 (2012)		Burton-Jeangros et al. (2017); Altobelli et al. (2019)
Tajikistan	Opportunistic	2009	> 20	Cytology		NR		10–50 (2015)		Altobelli et al. (2019); Aimagambetova et al. (2021)

Table 2.3 (continued)

Country or region	Type of programme	Start year	Target age range (years)	Primary screening method (age group)	Triage test[a]	Interval (age group) (years)	Invitation coverage (%)[b] (year)	Examination coverage (%) (year)	Participation rate (%) (year)	References
Turkey	Population-based	2004	30–65	HPV test	HPV16/18 genotyping and cytology	5		35 (2017)		Altobelli et al. (2019); Gultekin et al. (2019); Maver & Poljak (2020)
Turkmenistan	Opportunistic	2007	> 20	Cytology		1				Altobelli et al. (2019); Aimagambetova et al. (2021)
Ukraine	Opportunistic	NR	18–65	Cytology		1		73.7 (2003)		Rogovskaya et al. (2013); Altobelli et al. (2019)
United Kingdom	Population-based	1988	25–64	HPV test	Cytology	3 (25–49) 5 (50–64)	102.1 (2013)	62.5 (2013)	48.2–58.7[r] (2013)	Ponti et al. (2017); Basu et al. (2018); Maver & Poljak (2020)
Uzbekistan	Opportunistic	2010	25–49	Cytology		NR				Altobelli et al. (2019); Aimagambetova et al. (2021)

HPV, human papillomavirus; NR, not reported.

[a] Information not available for all countries. In countries with primary HPV screening, the triage strategy for women with a positive primary HPV screening test result generally involves two-step (follow-up or delayed) triage. Only the first step (reflex triage) is shown in the table.

[b] Invitation coverage for the age group 30–59 years for European Union Member States.

[c] In Belgium, only the Flemish region has a programme.

[d] In Denmark, HPV screening is gradually being implemented nationwide.

[e] Some municipalities target women younger than 30 years.

[f] Primary screening is predominantly cytology but can also be HPV testing.

[g] HPV triage after abnormal cytology; cytology triage after positive HPV test.

[h] In France, programmes were introduced in a few departments as from 1991; a national programme was launched in 2018. France transitioned to HPV primary screening in 2020. Data for examination coverage, screening coverage, and participation rate are from 13 departments.

[i] The screening interval is 3 years if the first two tests done 1 year apart are normal.

[j] In Germany, the Cancer Screening and Registry Act of 2013 created a legal framework to turn the current opportunistic screening for cervical cancer into organized population-based programmes. The Cancer Screening and Registry Act regulates data linkage between screening programmes and cancer registries (epidemiological or clinical). Since 2018, Germany has been transitioning to an organized population-based screening programme.

[k] HPV triage after abnormal cytology.

[l] Cytology or HPV16/18 genotyping after positive HPV test.

[m] Malta is implementing a pilot programme that targets a narrow age group.

[n] Age range: 30–60 years (65 years if HPV-positive at the last HPV test).

[o] In North Macedonia, a pilot programme with invitation letters was first introduced in four municipalities; this was rolled out nationally in 2012.

[p] Different target ages are reported by Davies & Dimitrievska (2015).

[q] In Romania, there is an organized population-based programme in some regions.

[r] Participation rate in the United Kingdom: England, 58.7%; Northern Ireland, 48.2%.

As of July 2019, the Netherlands and Turkey were the only two European countries with fully implemented national primary HPV-based cervical cancer screening (Maver & Poljak, 2020). In the Netherlands, the new primary HPV-based programme (established in 2017) covers all women aged 30–60 years (65 years if they were HPV-positive at the previous screening). Turkey redesigned its screening programme in 2014, introducing a revamped call–recall system and the use of primary HPV screening with a well-defined protocol outlining the management algorithms (Gultekin et al., 2019; Maver & Poljak, 2020). Finland, Italy, Sweden, and the United Kingdom (Wales) have implemented regional primary HPV screening (Maver & Poljak, 2020). Several other countries, including Belgium, Denmark, France, Germany, Ireland, Malta, and Norway, are in the process of implementing primary HPV screening (Haute Autorité de Santé, 2019; Hillemanns et al., 2019; Partanen et al., 2019; French Government, 2020; HSE, 2020; Maver & Poljak, 2020).

Some countries offer self-sampling kits for HPV testing to underscreened women. In the Netherlands, women who do not respond to the invitation letter within 4 months can request a self-sampling kit (van der Veen, 2017). Furthermore, women who are eligible for screening but do not want to visit their physician for a cervical sampling can request a self-sampling kit as a primary cervical cancer screening tool (van der Veen, 2017; RIVM, 2020). In Sweden, a self-sampling kit is offered to long-term non-attenders (Regionala Cancercentrum, 2019). In Denmark, self-sampling will be offered on an opt-in basis to all women as part of their second reminder for screening (sent 6 months after the initial invitation) (Tranberg & Andersen, 2018; Tranberg et al., 2018). In France, the national guidelines on primary HPV screening recommend that self-sampling should be offered to underscreened women (Haute Autorité de Santé, 2019).

(iii) Target age range and screening interval

In the EU, as recommended in the European guidelines, most countries have stopped cervical screening in women younger than 25 years and have increased the screening intervals to 3–5 years (Ponti et al., 2017; Basu et al., 2018). However, some heterogeneity still exists. In countries with population-based programmes, Czechia is the only country to screen women younger than 20 years. Most countries with cytology-based primary screening programmes use an interval of 3 or 5 years, except for Czechia and Germany, which have continued with yearly screening. Programmes based on primary HPV screening generally start at a later age and use 5-year intervals, although a 3-year interval has been retained in Sweden and the United Kingdom (for women younger than 50 years) and in Ireland (for women younger than 30 years).

Annual cytology was introduced in the former Soviet Union in the early 1960s and is still performed to a certain extent in Belarus, Ukraine, and the Russian Federation (Rogovskaya et al., 2013). The latest guidelines issued in the Russian Federation in 2017 are mostly in line with international recommendations (cytology every 3 years from age 30 years to age 60 years) (Barchuk et al., 2018). However, detailed information on quality, actual screening interval, and coverage is not currently available.

(iv) Invitation coverage, screening coverage, and participation rate

A survey among EU and European Free Trade Association (EFTA) Member States showed that organized efforts for quality assurance, monitoring, and evaluation are implemented to a different extent across European countries and that key performance indicators, such as coverage and participation, are not estimated in a comparable manner between most countries (Elfström et al., 2015). Cross-country comparisons should therefore be interpreted with caution.

In 12 of the European countries with population-based cervical cancer screening programmes, women who have undergone opportunistic screening within the recommended interval are excluded from invitations to screening; this reduces wastage of resources and improves programme efficiency (Ponti et al., 2017; Vale et al., 2019b). By design, these countries will have invitation coverage below 100%; because of this, comparisons of invitation coverage between countries could be misleading unless due consideration is given to the presence of opportunistic screening and related invitation strategies. The mean invitation coverage of women aged 30–59 years in the population-based cervical cancer screening programmes was 59.2%. The rate increased to 78.2% after adjusting for the population of the regional programmes (Vale et al., 2019b).

In the 15 European countries that have implemented population-based programmes and have provided data, the screening coverage (for the index year 2013) was 45.5% overall and ranged from 9.2% (Romania) to 86.3% (Sweden).

The participation rate in the European countries that provided data was 40.8% overall and ranged from 10.3% (Croatia) to 67.4% (Finland) (Ponti et al., 2017). However, as mentioned above, these results must be interpreted in the context of differing invitation strategies between the countries and the fact that opportunistic activity is frequently substantial in Europe.

2.2.4 WHO Region of the Americas: North America

Although Mexico is considered to be part of North America, most Pan American Health Organization (PAHO) reports consider Mexico as part of Latin America (PAHO, 2019, 2020a, b), and so Mexico is presented in Section 2.2.5. Puerto Rico, defined as a self-governing commonwealth in association with the USA, is presented independently for some reports,

although it is sometimes excluded from analyses because the data are insufficient.

(a) Health systems, policies, and guidelines

The Canadian federal government is the single payer for health services in the country and, through the Canada Health Act, defines the basic principles and rules that the provincial and territorial health insurance plans must follow to receive public funding (Martin et al., 2018). Provincial and territorial governments determine coverage of medically necessary services in consultation with their respective physician colleges and groups (Government of Canada, 2019).

At the national level, two major initiatives support cervical cancer screening in Canada: the Canadian Strategy for Cancer Control, launched in 2006, and the Canadian Partnership Against Cancer (CPAC), launched in 2007. They developed a strategy to implement organized screening programmes and to monitor cancer system performance (Canadian Strategy for Cancer Control, 2006; Canadian Partnership Against Cancer, 2020).

CPAC launched an updated strategy for the period 2019–2029, in which a main priority was to "diagnose cancer faster, accurately and at an earlier stage" and a key action was to strengthen existing screening efforts to ensure that the right people are getting screened and to eliminate barriers to participation in screening, particularly in hard-to-reach communities. For these communities, CPAC suggested that self-sampling for HPV testing for cervical cancer screening should be pursued as a strategy in Canada (Canadian Partnership Against Cancer, 2019).

The cervical cancer screening guidelines were updated in 2013 by the Canadian Task Force on Preventive Health Care (Canadian Task Force on Preventive Health Care, 2019). In these guidelines cytology-based screening was recommended every 3 years for women aged 25–69 years (Dickinson et al., 2013). More recently, the

Canadian Agency for Drugs and Technologies in Health recommended the replacement of primary cytology screening with HPV testing using 5-year testing intervals for women aged 25–69 years, and using a test with genotyping capability (CADTH, 2019). Nonetheless, cytology remains the primary screening test in Canada.

In the USA, citizens obtain health insurance through employers, independently through private purchase, or through government programmes (Zhao et al., 2020). The delivery of cervical cancer screening is mostly opportunistic and generally occurs in private-practice settings or through medical practitioners operating in federal, state, and local programmes (Kim et al., 2015). Although there are pockets of integrated health-care delivery systems that serve populations, there are few linkages between them, resulting in care that is often fragmented and is not coordinated at state or national levels (Habbema et al., 2012). The National Breast and Cervical Cancer Early Detection Program (NBCCEDP), operated by the Centers for Disease Control and Prevention (CDC), fully or partially funds breast and cervical cancer screening, diagnostic, and treatment services for eligible low-income, uninsured, and underinsured women. NBCCEDP also provides patient navigation services to help women overcome barriers and get timely access to high-quality care (Centers for Disease Control and Prevention, 2019). In addition, Medicare and Medicaid beneficiaries are covered for routine cervical cancer screening (American Cancer Society, 2021).

The Patient Protection and Affordable Care Act (ACA) (U.S. Legislative Counsel, 2010), a major health system reform signed into law in 2010, carried significant implications for access to cancer screening by way of health insurance expansion and changes in health insurance coverage. Health insurance expansion included coverage to dependents until the age of 26 years, extended income thresholds for Medicaid eligibility, and the establishment of mechanisms to increase the affordability of health insurance for the general population. Changes in health insurance coverage involved the inclusion of preventive services as part of the essential health benefits and the elimination of cost-sharing for certain preventive services (Sabik & Adunlin, 2017; Zhao et al., 2020). Several medical or cancer societies provide independent clinical guidelines. The most prominent cervical cancer screening guidelines include those of the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, the American Society for Clinical Pathology, the American College of Obstetricians and Gynecologists, and the United States Preventive Services Task Force (USPSTF) (Table 2.4).

(b)   Screening programmes and practices

Cervical cancer screening is well established in the USA and Canada. An overlap of organized and opportunistic screening exists in the USA, whereas in Canada cervical cancer screening is provided mostly through organized programmes with invitation and reminder systems. Thus, with some variability, population-based screening is available in most Canadian provinces, and for provinces and territories without organized programmes (Northwest Territories, Nunavut, Quebec, and Yukon), opportunistic screening is available through primary care providers (Canadian Partnership Against Cancer, 2018; Table 2.5). Cervical cancer screening is considered to be a medically necessary service in all provinces and territories and is free to Canadian citizens and residents at the point of care (Kiran et al., 2015).

In the USA, interpretation of and adherence to guidelines by primary care physicians vary widely, which has relevant impact on individual practices (e.g. overscreening, geographical and sociodemographic differences) (Yabroff et al., 2009; Hirth et al., 2013; Kepka et al., 2014; Porter Novelli, 2015; Cooper & Saraiya, 2017; Goding Sauer et al., 2020).

Table 2.4 Cervical cancer screening guidelines from cancer societies in the USA

Recommendation	Reference		
	American College of Obstetricians and Gynecologists (2016)	US Preventive Services Task Force (2018)	American Cancer Society (2020)
Age range			
Starting age (years)	21	21 Recommend against screening at younger ages	25
Stopping age (years)	65 if adequate negative screening within the past 10 yr[a]	65 if adequate negative screening within the past 10 yr[a]	65 if adequate negative screening within the past 20 yr[a]
Screening tests	HPV and cytology co-testing (ages 30–65) Cytology (ages 21–65)	Primary HPV testing (ages 30–65) HPV and cytology co-testing (ages 30–65) Cytology (ages 21–65)	HPV (preferred test) (ages 25–65) HPV and cytology co-testing (acceptable) (ages 25–65) Cytology (acceptable) (ages 25–65)
Screening interval for primary test			
HPV testing	Not more frequent than every 3 yr	Every 5 yr	Every 5 yr
Co-testing	Every 5 yr	Every 5 yr	Every 5 yr
Cytology	Every 3 yr	Every 3 yr	Every 3 yr
Screening for HPV-vaccinated women	As per the general guidelines	As per the general guidelines	As per the general guidelines
Screening for HIV-positive women	As per DHHS–CDC guidance	As per DHHS–CDC guidance	As recommended by CDC, NIH, and HIVMA

CDC, Centers for Disease Control and Prevention; DHHS, Department of Health and Human Services; HIVMA, HIV Medicine Association of the Infectious Diseases Society of America; HPV, human papillomavirus; NIH, National Institutes of Health; yr, year or years.

[a] Adequate negative screening could be either 3 consecutive Pap smears or 2 consecutive HPV tests. Guidance by the DHHS and the CDC for HIV-positive women comprises first screening 1 year after sexual onset and no later than age 21 years, or first screening on HIV diagnosis for women 21 years and older. Screening to be done with annual cytology or triennial HPV–cytology co-testing within the same age ranges as the general population.

Table compiled by the Working Group.

Table 2.5 Policies and practice for cervical cancer screening in the provinces and territories of Canada

Province or territory	Screening method	Start year of organized programme	Starting age (years)	Stopping age (years)	Interval (years)
Alberta	Cytology	2000	25	69	3
British Columbia	Cytology	1960	25	70	3
Manitoba	Cytology	2000	21	69	3
New Brunswick	Cytology	2014	21, or 3 yr after sexual onset	69 if ≥ 3 negative tests in 10 yr	1–1–1–2 or 3
Newfoundland and Labrador	Cytology	2003	21	70 if ≥ 3 negative tests in 10 yr	1–1–1–3
Northwest Territories	Cytology	NA	21	69	1–1–1–2
Nova Scotia	Cytology	1991	21	70	3
Nunavut	Cytology	NA	21 if sexually active	69	3
Ontario	Cytology	2000	21 if sexually active	70 if ≥ 3 negative tests in 10 yr	3
Prince Edward Island	Cytology	2001	21 if sexually active	65 if ≥ 3 negative tests in 10 yr	2
Quebec	Cytology	NA	21	65 if ≥ 2 negative tests in 10 yr	2 or 3
Saskatchewan	Cytology	2003	21, or 3 yr after sexual onset	69	2–2–2–3
Yukon	Cytology	NA	No data		

NA, not applicable; yr, year or years.
Adapted from Canadian Partnership Against Cancer (2018).

Table 2.6 Coverage of cervical cancer screening in North America

Age group (years)	Coverage (%)[a]	
Canada (2011–2013)		
	Hysterectomy corrected	Not hysterectomy corrected
21–29	73.6	77.9
30–39	76.6	76.3
40–49	77.2	68.6
50–59	71.9	59.9
60–69	63.7	47.6
Overall	73.5	67.1
USA (2018) (hysterectomy corrected[b])		
	All states and District of Columbia (without territories)	Puerto Rico
21–30	66.6	60.2
31–40	84.9	82.5
41–50	83.4	85.7
51–60	81.6	80.5
61–65	75.6	77.9
Overall	79.5	80.6

[a] Coverage is defined as women having at least one test in a 3-year period.
[b] Hysterectomy correction indicates the exclusion of women with history of hysterectomy from the analysis.
Data from: Canada (Canadian Partnership Against Cancer, 2016); USA (Centers for Disease Control and Prevention, 2015).

(c)   Performance of screening programmes

On the basis of the 2006 Strategy for Cancer Control and under the guidance of the performance monitoring indicators defined by the Public Health Agency of Canada in 2009 (PHAC, 2009), the Pan-Canadian Cervical Cancer Screening Network, established in 2010, has produced three reports on performance measures for cervical cancer screening, for the periods 2006–2008, 2009–2011, and 2011–2013 (Canadian Partnership Against Cancer, 2016). Age-adjusted coverage of cervical cancer screening in Canada for 2011–2013 is summarized in Table 2.6.

In the USA, monitoring of Healthy People 2020 goals is done through the National Health Interview Survey, which is a household survey with national representation, and surveillance of cytology coverage at the state level is done mainly through the Behavioral Risk Factor Surveillance System, which is a telephone survey; both surveys allow self-reporting of participation in cervical cancer screening (Centers for Disease Control and Prevention, 2015; Centers for Disease Control and Prevention, National Center for Health Statistics, 2020). In addition, the NBCCEDP and Medicare report cervical cancer screening participation on the basis of claims made to each funding programme (Centers for Disease Control and Prevention, 2019); likewise, several studies have analysed the impact of ACA on the use of cancer screening services based on national surveys and administrative claims (Zhao et al., 2020).

Cervical cancer screening coverage in the USA in 2018 is summarized in Table 2.6. Coverage was highest in women aged 31–40 years (84.9%) and lowest in women younger than 30 years (66.6%) (Table 2.6). Puerto Rico reported higher coverage than the average for the USA (80.6%). In 2012, women aged 18–64 years were eligible for the NBCCEDP; the percentage of screened women aged 40–64 years, by state, ranged from 5.0% to 73.2% (Tangka et al., 2015). Medicare follows the guideline recommendations and eligible

women are those aged 21–64 years; coverage by state ranges from 35.3% to 72.0% ([Medicaid/ CHIP, 2019](#)). As noted earlier, despite the high self-reported coverage in national surveys, the percentage of underserved screened women eligible for government-funded programmes remains low.

2.2.5 WHO Region of the Americas: Latin America and the Caribbean

(a) Health systems, policies, and guidelines

Most Latin American countries have segmented health systems, characterized by the coexistence of different organizational structures serving different population groups, under different rules and benefit packages, typically divided by socioeconomic and employment conditions ([Frenk & Gómez-Dantés, 2018](#)). Under segmented models, health care is provided to the lowest-income populations through public hospitals, employees are served by social security institutions, and the highest-income population is privately insured ([Frenk & Gómez-Dantés, 2018](#); [Kanavos et al., 2019](#)).

Some countries, such as Cuba and Costa Rica, have universal health systems with public funding and health care delivered by a single public institution ([Frenk & Gómez-Dantés, 2018](#); [Kanavos et al., 2019](#)). Other countries, such as Brazil and Colombia, have universal health systems with public contract models, in which health care is delivered by public and private institutions via direct contract with the public funding agency (as in Brazil) or via intermediary, mostly private, insurance companies (as in Colombia) ([Frenk & Gómez-Dantés, 2018](#); [Kanavos et al., 2019](#)).

In addition, some countries have adopted health benefit packages with explicit inclusion of cervical cancer screening and treatment of precancerous lesions and invasive cancer ([Giedion et al., 2014](#)).

Stewardship, which involves setting the rules for all actors and defining strategic directions for the health system as a whole (including cancer control), is separated and unequal in segmented models; in universal systems, this function is served by the ministry of health ([Frenk & Gómez-Dantés, 2018](#)). Despite limited stewardship to align rules and priorities *between* population segments, segmented models may have more coordinated health-care delivery *within* population segments than public contract models with indistinct participation of private and public institutions ([Frenk & Gómez-Dantés, 2018](#)). Together, the limitations of both model types make implementing organized cervical cancer screening a challenge in most Latin American countries.

Up to 2019, all countries in the Latin American region had defined recommendations or policies for cervical cancer screening, and 16 of 19 had updated their recommendations during the previous decade ([Table 2.7](#)). Furthermore, according to the WHO Cancer Country Profile survey, only two of 19 Latin American countries (Bolivia and Honduras) reported that they did not have a cervical cancer screening programme to implement recommendations, whereas 12 reported that they had organized population-based screening ([WHO, 2020c](#)). In the English-speaking Caribbean region, information on cervical cancer screening policies is available for only 12 of 21 countries ([Table 2.7](#)).

Some countries in the region have government institutions, departments, or official networks dedicated to the assessment of health technology and the development of clinical guidelines: Chile, ETESA ([Ministério de Salud de Chile, 2017](#)); Brazil, REBRATS ([Ministério da Saúde do Brasil, 2020](#)); Colombia, IETS ([IETS, 2020](#)); and Mexico, CENETEC ([Secretaría de Salud de México, 2020](#)). However, current recommendations for cervical cancer screening are derived mainly from national consensus, led

Table 2.7 Policies and practices for cervical cancer screening in countries of Latin America and the Caribbean

Country	Programme characteristics					Coverage[a]			References
	Year of last update to programme	Screening method	Target age range (years)	Interval (years)	Age range (years)	Coverage (%)	Coverage definition (years)	Year of report	
Latin America									
Argentina	2015	Cytology HPV test	25–29 30–64	1–1–3 5	25–64 35–49	70.3 72.5	2	2019	Arrossi et al. (2015); Ministerio de Salud de Argentina (2019)
Bolivia (Plurinational State of)	2009	Cytology VIA	25–64 NA	1–1–3 NA	25–64 35–44	NA 47.3	3	2008	Ministerio de Salud y Deportes Bolivia (2009a, b)
Brazil	2016	Cytology	25–64	1–1–3	25–64 35–44	79.4 91.6	3	2016	Ministério da Saúde do Brasil (2016, 2017)
Chile	2015	Cytology HPV test	25–29 30–64	3 5	25–64 35–44	72.9 76.0	3	2017	Ministerio de Salud de Chile (2015); Ministerio de Desarrollo Social de Chile (2018); Ministerio de Desarrollo Social y Familia de Chile (2018)
Colombia	2018	Cytology HPV test VIA/VILI	25–29 30–65 30–50	3 5 3	21–69 30–49	76.2 81.9	3	2015	Ministerio de Salud y Protección Social de Colombia (2015, 2018, 2019)
Costa Rica	2007	Cytology	≥ 20	2	25–64 35–44	74.1 78.3	3	2006	Ministerio de Salud de Costa Rica (2006, 2007); Hernández Villafuerte & Sáenz Vega (2006)
Cuba	2018	Cytology	25–64	3	25–64 30–44	NA 85.0	3	2014	Ministerio de Salud Pública de Cuba (2018); Bonet Gorbea & Varona Pérez (2014)
Dominican Republic	2010	Cytology	35–64	1–1–3	35–64 15–49	NA 54.8	2	2014	Rojas Gómez et al. (2010); CESDEM & ICF International (2014)
Ecuador	2017	Cytology HPV test	21–65 30–65	3 5	21–65 15–49	NA 55.9	2	2015	Espinosa et al. (2017); Freire et al. (2015)
El Salvador	2015	Cytology HPV test	20–29, 60–65 30–59	2 NA	20–65 30–49	NA 70.9	2	2008	Ministerio de Salud de El Salvador (2015); ADS CCI, CDC (2009)

Table 2.7   (continued)

Country	Programme characteristics					Coverage[a]			References
	Year of last update to programme	Screening method	Target age range (years)	Interval (years)	Age range (years)	Coverage (%)	Coverage definition (years)	Year of report	
Guatemala	2014	Cytology HPV test VIA	25–54 30 25–54	3–5 5 3–5	NA	NA	NA	NA	Ministerio de Salud Pública y Asistencia Social de Guatemala (2020)
Honduras	2015	VIA HPV test	25–30 30–64	3 5	25–64 35–44	NA 60.3	3	2002	Secretaría de Salud de Honduras (2015); Secretaría de Salud, Instituto Nacional de Estadística & ICF International (2013)
Mexico	2013	Cytology HPV test	25–64 35–64	3 5	25–64 35–44	36.4 38.7	1	2018	Secretaría de Salud de Mexico (2013); CNEGSR (2015); CIEE (2019)
Nicaragua	2010	Cytology VIA	25–64 30–50	1–1–1–3 1	25–64 35–44	NA 60.4	2	2014	Ministerio de Salud de Nicaragua (2010); PAHO (2010); INIDE & MINSA (2014)
Panama	2017	Cytology HPV test VIA	21–70 25–64 NA	2 3 NA	NA	NA	NA	NA	Ministerio de Salud & Caja de Seguro Social de Panamá (2017)
Paraguay	2015	Cytology HPV test	21–65 30–65	1–1–3 5	21–65 35–44	NA 57.2	2	2008	Barrios Fernández et al. (2015); Ministerio de Salud Pública y Bienestar Social de Paraguay, (2017a, b); CEPEP (2009)
Peru	2017	Cytology HPV test VIA	30–49 50–64 30–49	5 3 3	30–64 30–59	NA 57.4	3	2014	Ministerio de Salud de Perú (2019); INEI (2014)
Uruguay	2014	Cytology	21–69	1–1–3	21–64	78.4	3	2013	Muniz et al. (2015); Ministerio de Salud Pública de Uruguay (2018)
Venezuela	NA	Cytology	25–64	1–1–3	NA	NA	NA	NA	Murillo et al. (2016)
Caribbean									
Antigua and Barbuda	NA	Cytology HPV test	21–65 ≥ 30	5 NA	NA	NA	NA	NA	Bruni et al. (2019c)

Table 2.7 (continued)

Country	Programme characteristics				Coverage[a]				References
	Year of last update to programme	Screening method	Target age range (years)	Interval (years)	Age range (years)	Coverage (%)	Coverage definition (years)	Year of report	
Bahamas	NA	Cytology	≥ 21	1	20–64 30–49	66.2 66.3	2	2011	PAHO (2013); Bahamas Ministry of Health (2011); WHO (2020a)
Belize	2016	Cytology VIA	> 25 25–49	3 3	NA	NA	NA	NA	Ministry of Health Belize (2016)
Dominica	NA	Cytology	18–65	NA	NA	NA	NA	NA	Luciani et al. (2017)
Grenada	NA	Cytology	> 21	1–1–1–3	NA	NA	NA	NA	Bruni et al. (2019c)
Guyana	2010	Cytology VIA	Sexually active 25–49	NA	NA	NA	NA	NA	Maternal and Child Health Integrated Program (2012); PAHO (2013); Ministry of Health Guyana (2020)
Jamaica	2011	Cytology	18–65	1–1–3	18–65 35–44	NA 56.4	3	2010	Ministry of Health Jamaica (2011); Serbanescu et al. (2010)
Saint Kitts and Nevis	NA	Cytology	18–55	1–1–3	18–55 35–44	NA 72.3	2	2008	PAHO (2013); Luciani et al. (2017); WHO (2020a)
Saint Lucia	NA	Cytology	18–55	1	NA	NA	NA	NA	Luciani et al. (2017); Bruni et al. (2019c)
Saint Vincent and the Grenadines	NA	Cytology VIA	18–60 NA	1–1–3 NA	18–69 30–49	58.6 70.9	Ever	2015	PAHO (2013); Luciani et al. (2017); WHO (2020a)
Suriname	2012	Cytology VIA	Postmenopausal women 23–55	2 2	NA	NA	NA	NA	PAHO (2013)
Trinidad and Tobago	NA	Cytology	> 18	1	> 18 35–44	NA 36.6	2	2012	PAHO (2013); Luciani et al. (2017); WHO (2020a)

HPV, human papillomavirus; NA, not available; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine; VIA/VILI, VIA followed by VILI in case of positive VIA result.

[a] Coverage is defined as the percentage of women with a history of participation in screening within the indicated period for the corresponding age range.

by the ministries of health, without systematic development. Chile and Colombia have national guidelines based on systematic review of scientific evidence (Ministerio de Salud y Protección Social de Colombia, 2014; Ministério de Salud de Chile, 2015), and in Mexico, the Mexican Institute of Social Security has developed systematic guidelines for its affiliated institutions (Instituto Mexicano del Seguro Social, 2011).

(b) Screening programmes and practices

Latin American countries have a long-standing tradition in cervical cancer screening. Initially led by nongovernmental organizations (NGOs) in the 1950s and 1960s (mainly Leagues Against Cancer), the first national programmes were introduced in the early 1990s (Murillo et al., 2008). Today, cervical cancer screening is available in all Latin American countries; however, the region contends with large social disparities, and a significant number of women do not have access to proper health care (Murillo, 2019). Most countries in the region have updated their screening recommendations during the past decade and have made significant progress in introducing either molecular testing or screen-and-treat approaches (Table 2.7).

Screen-and-treat approaches are recommended for hard-to-reach women in eight Latin American countries. Most of these are based on VIA, but in Colombia a combination of VIA and visual inspection with Lugol's iodine (VILI) is recommended, in El Salvador HPV test-and-treat is recommended, and in Paraguay colposcopy followed by large loop excision of the transformation zone (LLETZ) is recommended (Table 2.7).

Most countries in Latin America start screening at age 25 years; in the Caribbean, screening generally starts at adulthood (18 years and older) or onset of sexual activity. Nonetheless, some countries in Latin America endorse screening in adolescents, depending upon assessment of individual risk. Currently, three of the six countries that recommend screening women younger than 25 years – Costa Rica, El Salvador, and Panama – also recommend a more frequent screening interval (2 years) (Table 2.7).

(c) Performance of screening programmes

Comprehensive programme reports are not available for Latin America and the Caribbean. The data on cervical cancer screening coverage reported in Table 2.7 are derived from population-based surveys, and data on other programme performance indicators are from published studies in scientific journals. In several countries, the surveys are not aligned with screening programmes, because target ages and screening intervals are not concordant. Some countries may have reached or may be close to reaching the target of the WHO Global Strategy for the Elimination of Cervical Cancer as a Public Health Problem (70% coverage for women aged 35–45 years); coverage ranges from 66.3% in the Bahamas to 85.0% in Cuba. For Argentina and Brazil, information is available for similar age ranges, but these require careful interpretation because the data are restricted to urban populations (Arrossi et al., 2015; Ministério da Saúde do Brasil, 2017).

A major challenge in the region is the compliance with follow-up for women with a positive screening test result. Some studies show that follow-up compliance has a greater impact than population screening coverage on cervical cancer mortality (Murillo et al., 2008; Chocontá-Piraquive et al., 2010). Follow-up rates for women with a positive screening test result in selected studies in Latin American countries are given in Table 2.8; however, differences in settings, populations, and methods make comparisons between countries difficult (Austad et al., 2018; Arrossi et al., 2019).

Table 2.8 Follow-up rates[a] for women with a positive screening test result from selected studies in countries in Latin America

Country	Study level	Sector	Screening method	Follow-up rate (%)	References
Programme data					
Argentina	Regional	Public	Cytology	65.5	Arrossi et al. (2019)
			HPV (clinician)	79.2	
			HPV (self-sampling)	75.0	
Brazil	Local	Public	Cytology	35.0	Araújo et al. (2014)
Chile	Local	Public	HPV and cytology triage	71.1	Melo et al. (2014)
Guatemala	Regional – Indigenous	Public	Cytology	88.7	Austad et al. (2018)
Nicaragua	Local	Public	Cytology	58.0	Vastbinder et al. (2010)
Self-reported					
Colombia	Regional	All	Cytology	72.2	Wiesner et al. (2010)
Guatemala	Regional – Indigenous	Public	Cytology	42.6	Austad et al. (2018)

HPV, human papillomavirus.
[a] Follow-up rates are estimates based on women at risk for every step in the screening algorithm as reported in the original source: screening-positive to triage or colposcopy or biopsy, triage-positive to colposcopy or biopsy, diagnosis of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) or high-grade squamous intraepithelial lesion (HSIL) to treatment. Usually follow-up increases in the later phases of the algorithm.

2.2.6 WHO South-East Asia Region

The data on screening activities are limited for some countries in this region (Table 2.9). Four countries – Bhutan, Maldives, Sri Lanka, and Thailand – have population-based cervical cancer screening programmes. Other countries have initiated screening activities on an opportunistic basis, using mostly VIA but also cytology as a primary screening test. Where screening is available, participation rates are usually low.

(a) Bangladesh

In 2004, the Government of Bangladesh initiated a VIA-based screening programme in collaboration with the United Nations Population Fund and Bangabandhu Sheikh Mujib Medical University (BSMMU) (Basu & Majid, 2008). VIA is used at upazila (subdistrict) health complexes, maternal and child welfare centres, district hospitals, medical college hospitals, and BSMMU and is provided by trained family welfare visitors, senior staff nurses, and physicians (Basu & Majid, 2008; Basu et al., 2010; Nessa et al., 2010).

(b) Bhutan

In 2000, the Ministry of Health Bhutan launched a national cytology-based screening programme; Pap tests are provided free of charge by trained female health assistants, nurses, and physicians in district, regional, and national referral hospitals through maternal and child health clinics, and in basic health units, where primary care services are offered. The screening coverage varies across the country, ranging from about 20% to 60% of the target population in different provinces (Baussano et al., 2014; Dhendup & Tshering, 2014; Ministry of Health Bhutan, 2014).

(c) Democratic People's Republic of Korea

The Democratic People's Republic of Korea has a national public health system that provides health-care services at no direct cost to the patient (UNICEF DPRK, 2006). Physicians, midwives, and nurses have the responsibility to carry out these services, but there is no published information on how this policy is implemented (Tran et al., 2011).

Table 2.9 Policies and practice for cervical cancer screening in countries of the WHO South-East Asia Region

Country	Type of programme or setting	Year of programme or guidelines	Target age range (years)	Interval (years)	Screening method	Participation rate (%)	References
Bangladesh	National	2004	> 30	NA	VIA	NA	Basu & Majid (2008)
Bhutan	National	2010	20–60	3	Cytology	20–60	Dhendup & Tshering (2014); Ministry of Health Bhutan (2014)
Democratic People's Republic of Korea	National	NR	30–60	1	Cytology	NA	Tran et al. (2011)
India	Opportunistic	2016	30–65	5	VIA	22	Ministry of Health and Family Welfare, Government of India (2016); Monica & Mishra (2020)
Indonesia	Pilot	2007	30–50	3–5	VIA	7.3	WHO (2017); Ministry of Health Indonesia (2019)
Maldives	Population-based	2014	30–50	5	VIA	NA	Ministry of Health Maldives (2016); Maldives UNFPA (2014)
Myanmar	National	2020 (expected)	30–49	3–5	VIA or HPV test	NA	WHO (2020b)
Nepal	Opportunistic	2010	30–60	5	VIA	2.8	Darj et al. (2019); ICO/IARC Information Centre on HPV and Cancer (2019)
Sri Lanka	National	1998	> 35	5	Cytology	34.6	Ministry of Health Sri Lanka (2014, 2019); Kumara & Dasanayake (2017)
Thailand	National	2005	30–60	5	Cytology or VIA	61	Khuhaprema et al. (2012); Department of Medical Services Thailand (2019); Ploysawang et al. (2021)
		2020	30–60	5	HPV test	NA	

HPV, human papillomavirus; NA, not applicable; NR, not reported; VIA, visual inspection with acetic acid.

(d) India

The 2016 operational guidelines for implementation of cancer screening in India recommended VIA screening every 5 years for women aged 30–65 years ([Ministry of Health and Family Welfare, Government of India, 2016](#)). Opportunistic screening using VIA is currently administered by female staff medical officers and staff nurses at primary health centres, alongside screening for oral cancer and breast cancer. Screening coverage in India remains low, and the average participation rate across districts has been reported to be about 22% ([Monica & Mishra, 2020](#)). As a result, cancers are detected primarily through opportunistic screening or after the onset of symptoms ([Ministry of Health and Family Welfare, Government of India, 2016](#)).

(e) Indonesia

The Indonesian Ministry of Health launched the Cervical and Breast Cancer Prevention project in 2007 as a pilot study in Karawang District ([Kim et al., 2013](#)). Women aged 30–50 years are eligible, and VIA is provided by trained healthcare providers, including nurses, general practitioners, and midwives in primary health centres ([Kim et al., 2013](#); [WHO, 2017](#); [Wahidin, 2018](#)). Screening is covered by the national health insurance system and is provided free of charge ([BPJS Kesehatan, 2014](#)). From 2007 to 2016, the programme was running in all 34 provinces (100%), 393 of 514 districts or municipalities (76%), and 3706 of 9813 primary health centres (38%) ([Wahidin, 2018](#)). The coverage of screening is low; in 2018, only 7.3% of the target population was screened ([Ministry of Health Indonesia, 2019](#)).

(f) Maldives

A population-based cervical cancer screening programme was launched in Maldives in 2014 by the ministry of health and gender with support from the United Nations Population Fund ([Maldives UNFPA, 2014](#)). The programme offers screening to women aged 30–50 years at an interval of 5 years using VIA as the primary screening test. Women with a positive test result are referred for diagnostic testing using colposcopy and subsequent treatment ([Ministry of Health Maldives, 2016](#)). In the absence of diagnostic facilities, women with a positive VIA test result are treated with cryotherapy in the same visit.

(g) Myanmar

Myanmar is one of the six LMICs selected by the United Nations Joint Global Programme on Cervical Cancer Prevention and Control (UNJGP) for support to implement a national cervical cancer screening programme between 2018 and 2021 ([WHO, 2020d](#)). As recommended by the UNJGP, National Guidelines on Secondary Prevention of Cervical Cancer for Public Health Sector Facilities were developed in 2018 and the National Programme for Secondary Prevention of Cervical Cancer is expected to run between 2020 and 2024. Currently, opportunistic screening services are offered in selected hospitals and pilot programmes are carried out mostly by NGOs.

(h) Nepal

The national guidelines for cervical cancer prevention in Nepal were formulated in 2010 ([Darj et al., 2019](#)). There is no organized national screening programme; however, the government actively organizes health camps and screening campaigns across the country ([Global Giving, 2021](#)). In addition, NGOs such as the Nepal Network for Cancer Treatment and Research (NNCTR) support cervical cancer screening by forming mobile teams of specialist nurses and community volunteers that travel to communities within the Kathmandu Valley area. Despite the efforts of the government and other parties, the coverage of cervical cancer screening in 2003 was very low, with only 2.8% of eligible women

screened (ICO/IARC Information Centre on HPV and Cancer, 2019).

(i) Sri Lanka

Cervical cancer screening by Pap test was established in Sri Lanka as a national programme in 1998 (Gamage, 2017). Pap test screening services are provided through the Well Woman Programme and the Family Health Bureau, Ministry of Health Sri Lanka. Sri Lanka has successfully implemented the Well Women Programme at the primary health care level through a network of more than 800 well woman clinics (Ministry of Health Sri Lanka, 2019). Public health midwives identify women aged 35–45 years and motivate them to attend the well woman clinics for routine primary and reproductive health care. Those with positive Pap test results are referred to a consultant gynaecologist for colposcopy (Ministry of Health Sri Lanka, 2019). In 2014, 34.6% of the target population received a Pap test at a well woman clinic (Ministry of Health Sri Lanka, 2014). The overall proportion of women aged 35 years who had attended a well woman clinic increased steadily, from 34.6% in 2014 to 61.6% in 2018 (Ministry of Health Sri Lanka, 2019).

(j) Thailand

After a pilot demonstration project implemented from 1999 to 2002, the National Cancer Institute of Thailand launched a national cervical cancer screening programme in 2005, in cooperation with the National Health Security Office, Department of Medical Services, and Department of Health (Khuhaprema et al., 2012; Department of Medical Services Thailand, 2019). Women aged 30–60 years receive cytology screening free of charge every 5 years through more than 10 000 primary care units and community-based health centres. VIA-based screening is also available in 29 provinces for women aged 30–45 years. Women with abnormal screening test results are referred for colposcopy,

biopsy, and treatment in provincial hospitals. Before the launch of the national screening programme, only 25% of Thai women had ever received screening. In 2014, 61% of the target population received screening; 98.9% of these received a Pap test and 1.1% received VIA. The National Health Security Office introduced HPV testing as primary screening in 2020, in place of Pap testing, at 5-year intervals for women aged 30–60 years (Department of Medical Services Thailand, 2019; Ploysawang et al., 2021).

2.2.7 WHO Western Pacific Region

The WHO Western Pacific Region includes countries with very different resource levels. Some high-income countries, such as Australia, New Zealand, the Republic of Korea, Singapore, and Taiwan, China, have well-established population-based cervical cancer screening programmes and use either HPV testing or cytology as the primary screening test. Other countries in the region have national guidelines and strategies in place, but no population-based screening programmes. These countries rely on opportunistic screening using VIA or cytology. Some countries, such as the Pacific Island nations, have implemented pilot screening projects (Table 2.10).

(a) Australia

A national cervical screening programme was established in Australia in 1991 to provide organized population-based cervical screening using biennial Pap tests for women aged 18–69 years (Cancer Council Australia, 2018; AIHW, 2019). In 2017, the programme transitioned from cytology-based to primary HPV-based testing with partial HPV genotyping and reflex liquid-based cytology (LBC) at 5-year intervals in a target population of women aged 25–74 years, in accordance with the Medical Services Advisory Committee recommendations. HPV self-sampling facilitated by a medical practitioner, nurse

Table 2.10 Policies and practice for cervical cancer screening in countries of the WHO Western Pacific Region

Country or territory	Type of programme or setting	Start year	Target age range (years)	Interval (years)	Screening method	Participation rate (%)	References
Australia	Population-based	1991 2017	18–69 25–74	2 5	Cytology HPV test	56.4 NA	Cancer Council Australia (2018); AIHW (2019)
Brunei Darussalam	National	2010	20–65	3	Cytology	56.3	Government of Brunei Darussalam (2020); Suhaimi et al. (2020)
Cambodia	Opportunistic	2014	30–49	NA	VIA	NA	WHO (2015)
China	National	2009	35–64	3	Cytology or VIA	31.4	Kang & Qiao (2014); Wang & Qiao (2015)
Hong Kong Special Administrative Region	Organized	2004	25–64	1–1–3	Cytology	60.5	Centre for Health Protection (2004, 2017)
Japan	Organized	1983	> 20	2	Cytology	33.7	Ministry of Health, Labour and Welfare Japan (2017); Hamashima (2018)
Malaysia	National	1998 2019	20–65 30–49	1–1–3 5	Cytology HPV test	12.8 NA	Ministry of Health Malaysia (2019)
Mongolia	Project	2012	30–60	3	Cytology	28	WHO (2014a)
New Zealand	Population-based	1990	25–69	3	Cytology and HPV co-testing	70.4	Ministry of Health New Zealand (2019); National Screening Unit New Zealand (2020a, 2021)
Philippines	Organized	2006	25–55	5–7	VIA or cytology	NA	Domingo & Dy Echo (2009)
Republic of Korea	Population-based	1999	> 30	2	Cytology	57	Lee et al. (2002); Kim et al. (2011); Hong et al. (2020)
Singapore	Population-based	2004 2019	25–69 > 30	3 5	Cytology HPV test	50.7 NA	Jin et al. (2013); Ministry of Health Singapore (2019); Government of Singapore (2020)
Taiwan, China	Population-based	1995	> 30	3	Cytology	72.1	Su et al. (2013); Ministry of Health and Welfare, Health Promotion Administration (2018)
Viet Nam	Pilot	2008	30–54	NA	Cytology	NA	Pham et al. (2019)

HPV, human papillomavirus; NA, not applicable; VIA, visual inspection with acetic acid.

practitioner, or other health-care professional is also available for underscreened or never-screened women. Data in the Australian population-based cancer registries are collected by state and territorial governments and compiled into the Australian Cancer Database. Women with test results positive for HPV16 or HPV18 are referred for colposcopy. If a woman's results are positive for other carcinogenic HPV types (not HPV16 or HPV18), LBC is used for triage to determine whether she should undergo colposcopy or repeat HPV testing in 12 months.

(b)   Brunei Darussalam

A cervical cancer screening programme in Brunei Darussalam was established in 2010 as part of a national health screening programme for major noncommunicable diseases (Lee et al., 2012; Government of Brunei Darussalam, 2020). Women aged 20–65 years who have not undergone screening in the previous 3 years are offered Pap testing in health centres or well woman clinics (Government of Brunei Darussalam, 2020). Screening tests are provided free of charge. Coverage was 56.3% in 2016 (Suhaimi et al., 2020).

(c)   Cambodia

Currently, no cervical cancer screening programme is available at the national level. In 2013, VIA screening and on-site treatment with cryotherapy was implemented at selected health centres after provision of training for midwives the previous year (WHO, 2015; Hav et al., 2016).

(d)   China

Between 2009 and 2011, the ministry of health, the ministry of finance, and the All-China Women's Federation made a first step towards nationwide provision of cancer screening with the launch of the National Cervical Cancer Screening Program in Rural Areas (NCCSPRA), which made cervical cancer tests available free of charge to 10 million women in 221 sites in rural China (Kang & Qiao, 2014; Wang & Qiao, 2015; Di, 2017). The programme was expanded to 1140 sites for 30 million women in rural areas between 2012 and 2015 (Wang & Qiao, 2015). Through the NCCSPRA, women aged 35–59 years were offered Pap testing or VIA at 3-year intervals (Kang & Qiao, 2014). Despite strong support for the screening programme from central government, only 8.4% of the target population received cervical cancer screening between 2009 and 2011 (Di, 2017). In 2015, the proportion of women aged 35–64 years who received screening increased to 31.4% (Zhang et al., 2018).

(e)   Hong Kong Special Administrative Region, China

A territory-wide organized cervical screening programme was launched by the Department of Health in collaboration with health-care providers in the public and private sectors in 2004. Through this programme, sexually active women aged 25–64 years are invited to undergo Pap testing every 3 years after having two consecutive normal annual Pap tests (Centre for Health Protection, 2004, 2019). The Cervical Screening Information System serves as the central registry for results from the cervical screening programme (Centre for Health Protection, 2004). Between 2014 and 2015, about 60.5% of the target population reported ever having a cervical Pap test (Centre for Health Protection, 2017).

(f)   Japan

In 1983, national organized cancer screening programmes were introduced in Japan based on the Health Service Law for the Aged; initially these included screening for cervical and gastric cancers, and breast, colorectal, and lung cancers were added later (Hamashima, 2018). According to the most recent National Cancer Center of Japan guidelines update (2013), cytology every 2 years is the primary test for cervical cancer

recommended for women aged 20 years and older. Since 1998, municipal governments have been responsible for implementing cancer screening programmes and collaborating with prefectural and national governments; this has resulted in deviations from national screening guidelines and differing approaches to programme organization at the municipal level (Sano et al., 2014; Sauvaget et al., 2016; Hamashima, 2018). Furthermore, because cancer preventive services are not included in the national health insurance system and are financed instead through municipal budgets, the extent of subsidy for screening tests varies (Sauvaget et al., 2016). In a 2016 national survey, the self-reported participation in cervical cancer screening in the previous 2 years in women aged 20–69 years was 33.7%; this figure includes both organized and opportunistic screening (Ministry of Health, Labour and Welfare Japan, 2017).

(g) Malaysia

The ministry of health launched a national Pap test screening programme in Malaysia in 1998 (Ministry of Health Malaysia, 2019). Through this programme, all eligible women aged 20–65 years can undergo Pap testing at 3-year intervals if they have had normal results for the first two annual tests. Screening is opportunistic; women are offered Pap tests when attending clinics for health screenings. About 75% of Pap tests are publicly funded and administered free of charge, whereas the remaining 25% are provided for a fee by university hospitals, private facilities, and NGOs. The guidelines were updated in 2019 to include primary HPV testing for sexually active women aged 30–49 years at 5-year intervals for those with a negative HPV test result. HPV self-sampling kits are available. Women with a positive test result for HPV16 or HPV18 are referred for colposcopy assessment. LBC is used for triage in women with a positive test result for other carcinogenic HPV types (not HPV16 or HPV18).

According to the National Health and Morbidity Survey, only 26% of eligible women received cervical cancer screening in 1996, 43.7% in 2006, and 12.8% in 2011 (Ministry of Health Malaysia, 2019).

(h) Mongolia

With support from the United States Millennium Challenge Corporation (MCC), cervical cancer screening via Pap testing at 3-year intervals was made available in Mongolia in 2012 for women aged 30–60 years through family clinics. The MCC project supported training for nurses and cytologists to administer and interpret Pap tests and provided equipment. In 2013, more than 70 000 women from the target group underwent cervical cancer screening; however, screening participation dropped to 56 000 (28%) in 2014, when the MCC project funding ended (WHO, 2014a).

(i) New Zealand

The New Zealand organized national cervical screening programme was established in 1990 (National Screening Unit New Zealand, 2020a). Although cytology remains the primary cervical cancer screening test, national guidelines for HPV and Pap co-testing were introduced in New Zealand in 2010. There are plans to adopt HPV testing (with self-sampling options) as the primary modality within the national cervical screening programme (National Screening Unit New Zealand, 2020b). The results of all cytology, colposcopy, and HPV tests are recorded in the national cervical screening programme register (National Screening Unit New Zealand, 2020a). In January 2021, it was reported that 70.4% of the target population had had a cervical cancer screening test in the previous 3 years (National Screening Unit New Zealand, 2021).

(j) The Philippines

The Philippines Department of Health established an organized cervical screening programme in February 2006 (Domingo & Dy Echo, 2009). In a target population of women aged 25–55 years, the programme recommended using VIA at least once in a 5- to 7-year interval in rural health units with no Pap test capability and using VIA as a triage tool before Pap test at district, provincial, and regional hospitals with Pap test capability. Women with positive or suspicious test results are referred for diagnosis and treatment in tertiary facilities. The organized programme includes sustainable capacity-building, training, education, and hiring of health workers.

(k) Republic of Korea

The Republic of Korea has a single-payer public insurer, the National Health Insurance Corporation (NHIC) (Kim et al., 2011). The NHIC operates the medical aid programme to cover health services for low-income individuals. The Korean organized national cancer screening programme was introduced in 1999 to provide cancer screening free of charge to medical aid recipients; in 2005, it was expanded to serve those in the lower 50% of the NHIC premium. People within the upper 50% of the NHIC premium receive screenings at 20% out-of-pocket cost. The national cervical screening programme is managed and monitored by the National Cancer Center, in cooperation with the NHIC. The national cervical screening programme Support and Evaluation Council developed screening guidelines in 2001, recommending Pap testing to women aged 30 years and older at 2-year intervals (Lee et al., 2002; Kim et al., 2011). The overall proportion of women up to date with cervical cancer screening has remained relatively stable: in 2004, 58% of eligible women had had a Pap test in the previous 2 years and in 2018, the figure was 57% (Hong et al., 2020).

(l) Singapore

CervicalScreen Singapore, the national cervical cancer screening programme for Singapore, was launched in 2004 (Jin et al., 2013). Women aged 25–69 years are invited to attend for subsidized Pap testing at 3-year intervals at government-funded polyclinics. The CervicalScreen Singapore registry was set up in 2004 to monitor the quality and evaluate the effectiveness of the screening programme; however, the registry does not capture screening data from outside the government-funded polyclinics or public hospitals (i.e. Pap tests performed at private clinics or hospitals). More women receive Pap testing at private clinics than at publicly funded polyclinics; this may be because private clinics have a greater market share in the provision of primary care services than the public polyclinics. The 2016 Health Behaviour Surveillance Survey showed that 50.7% of women in Singapore aged 25–69 years had had a Pap test in the previous 3 years (Government of Singapore, 2020). In 2019, the ministry of health introduced the HPV test as the primary screening test (in place of the Pap test) for women aged 30 years and older (Ministry of Health Singapore, 2019).

(m) Taiwan, China

The Bureau of Health Promotion of the Department of Health initiated a national cervical cancer screening programme in Taiwan, China, in 1995 (Chen et al., 2002; Su et al., 2013). The screening programme includes an information system, a quality control and monitoring system, and public health education for the general public. In 2017, 72.5% of women aged 30–69 years had received cervical cancer screening within the previous 3 years (Ministry of Health and Welfare, Health Promotion Administration, 2018).

(n) Viet Nam

There is no national cervical screening programme in Viet Nam; women are expected to seek out screening on an opportunistic basis, without reimbursement from the national health insurance system. Between 2008 and 2015, pilot screening programmes for cervical, breast, oral, and colorectal cancer were implemented with the support of various domestic and international partners. More than 100 000 women aged 30–54 years received a Pap test between 2008 and 2010. Opportunistic screening is generally available in hospitals, particularly in Hanoi and Ho Chi Minh City (Pham et al., 2019).

(o) Pacific Island nations

In the 21 Pacific Island nations, 11 countries and territories have cytology-based screening programmes, including Pap testing alone, HPV and Pap co-testing, or VIA and Pap co-testing (Obel et al., 2015). Ten of the countries and territories do not have formal screening policies; Papua New Guinea does have a screening programme with 1% coverage of the eligible population. Coverage rates vary widely: about 8% in Fiji, 50% in New Caledonia, and 100% in Tokelau. [However, it should be noted that these estimates have been self-reported by the countries and that monitoring mechanisms for screening are often weak in the region.]

2.3 Quality assurance of screening programmes

2.3.1 Description and role of quality assurance in screening programmes

According to the Institute of Medicine, quality is the extent to which health services for individuals and populations increase the likelihood of desired health outcomes that is consistent with the current scientific evidence (Institute of Medicine, 1990). Quality assurance measures the quality of the service delivered, ensuring that delivery of the screening programme provides beneficial outcomes to participants along the continuum of screening participation, recall, follow-up of abnormal results, and treatment of cervical precancers. Measuring the performance of a programme enables variability in service to be identified and adjustments to be made so that all participants in a screening programme have adequate care and outcomes (Institute of Medicine, 2001).

Quality assurance is particularly important in cancer preventive programmes, such as cervical cancer screening, in which very large populations of apparently healthy women are invited to participate to detect asymptomatic disease. Because of this, in addition to reducing the incidence of invasive cervical cancer (i.e. achieving health benefits), cervical cancer screening programmes have to consider an optimal benefit–harm balance, according to the best current scientific evidence (Gray et al., 2008).

Cancer prevention programmes are implemented within national health systems (WHO, 2014b). In 2007, WHO published a framework for health system strengthening, which included six health system building blocks: health service delivery; health workforce; health information systems; medical products, vaccines, and technologies; health financing; and leadership and governance. The achievements of a programme are then monitored with regard to the goals of improved health, responsiveness, social and financial risk protection, and improved efficiency (WHO, 2007). According to WHO, in addition to considering the health system building blocks, development and implementation of national cervical cancer prevention and control programmes includes the following phases: national policy and establishment of a programme management structure, programme planning and preparation, programme implementation, and programme monitoring and evaluation (WHO, 2014b).

Organized screening programmes have centralized responsibility for the performance of the programme and are responsible for carrying out programme monitoring and evaluation. According to WHO, monitoring is defined as the continuous oversight of an activity, whereas evaluation is defined as the systematic and objective assessment of the adequacy and effectiveness of the programme as it relates to its objectives (WHO, 2014b).

Performance standards are a means to improve outcomes. A standard defines the level of desired performance for a specific service on the basis of scientific evidence and best practices (WHO/PAHO, 2013). Performance indicators, also known as quality indicators or quality measures, are measurable evaluations of the ability of a screening programme to successfully deliver the desired level of performance (Table 2.11). Characteristics of a desirable performance measure include relevance, measurability, accuracy, and feasibility. Through monitoring and evaluation, the quality assurance process within a screening programme determines and measures performance indicators against desired targets (Institute of Medicine, 2001). For a screening programme to carry out comprehensive quality assurance measurements, timely data collection is required. Information technology infrastructure is necessary to facilitate this data collection, including a screening registry, which maintains screening records for individual participants and is linkable to a population-level cancer registry. The ability to create and maintain a robust data collection system may be challenging in LMICs. WHO has provided guidance documents for cervical cancer surveillance and monitoring in various health system environments (WHO, 2018).

An extensive list of suggested quality indicators has been provided by WHO; these are organized into global, core, and optional categories. The indicators are generally focused on screening, screening test results and referrals, treatment and referrals, programme and service delivery, facility and laboratory linkages, and HIV service integration (WHO, 2018).

2.3.2 Examples of quality assurance within screening programmes

(a) European Union

The 2008 European guidelines for quality assurance in cervical cancer screening programmes serve to inform EU Member States about how to create a robust screening programme and how to measure performance (Arbyn et al., 2008). Specifically, the guidelines state that attention should be paid not only to communication and technical aspects, but also to training and qualification of personnel, performance monitoring and audit, and evaluation of the impact of screening on the burden of the disease. The guidelines suggest 20 performance indicators, which are grouped into three categories: screening intensity, screening test performance, and diagnostic assessment and treatment. Organized efforts for quality assurance, monitoring, and evaluation differ across the EU, and key performance indicators, such as programme coverage and participation, are not comparable across countries (Elfström et al., 2015).

In 2017, Public Health England (PHE) published a guidance document for quality assurance of the National Health Service (NHS) cervical screening and colposcopy programme, which includes components of the programme, key stakeholders, data collection tools, and frequency of evaluation of the screening and colposcopy sites (Public Health England, 2017). Quality assurance of NHS programmes involves (i) assurance, in which the quality of screening services is measured against agreed-upon standards; and (ii) quality improvement, in which screening programmes are supported in increasing the quality of their services. Quality assurance is the responsibility of the PHE

Table 2.11 Performance indicators of cervical cancer prevention programmes

Screening intensity
- Participation is the percentage of eligible women who underwent cervical screening within a specified interval
- Retention is the percentage of eligible women re-screened after a negative screening test result within a specified interval
- Coverage of a target population
- Screening test consumption (Arbyn et al., 2008; Anttila et al., 2015)

Screening test performance
- Unsatisfactory specimen rate (applies to cytology)
- All screening test results, including abnormal results (PPV)

Descriptive indicators or burden of disease
- Pre-cancer detection rate is defined as the number of precancerous lesions, including HSIL, detected per 1000 women in a previous time frame
- Cancer incidence
- Screening history of cases of invasive cervical cancer
- Disease extent at diagnosis of invasive disease: cancer stage

Follow-up and management of screen-positive results
- Percentage of participants with high-grade screen results who are referred to and undergo colposcopy services

System capacity
- Turnaround time
- Time to colposcopy for participants with high-grade cytology results (± HPV results)

Colposcopy services
- Colposcopy referral rate
- Failure to attend colposcopy
- Retreatment proportion
- Biopsy rate: percentage of participants with a positive high-grade screen result who receive a histological diagnosis
- Number of new referral evaluations by colposcopist, number of colposcopies for high-grade referrals
- Proportion of women treated for LSIL or CIN1 (appropriateness)
- Reporting requirements at the time of colposcopic evaluation (Mayeaux et al., 2017): reason for referral, technical adequacy of colposcopic examination, colposcopic examination description, biopsy and proposed follow-up or management
- Timeliness

CIN1, cervical intraepithelial neoplasia grade 1; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; PPV, positive predictive value.

Screening Quality Assurance Service, and the quality assurance process consists of peer-review visits of screening sites every 3–5 years, production of data reports, expert advice and support of investigations, educational meetings, and targeted support to providers (Public Health England, 2017).

(b) USA and Canada

The United States Department of Health and Human Services Health Resources and Services Administration monitors cervical cancer screening as a measure of clinical quality. This measure is defined as the proportion of women aged 21–64 years who received at least one Pap test in the previous 1–2 years (U.S. Department of Health and Human Services Health Resources and Services Administration, 2019). The American Society for Colposcopy and Cervical Pathology has developed recommendations for colposcopy and biopsy for cervical cancer prevention, which include 11 quality indicators spanning documentation, biopsy protocols, and time intervals between index screening tests and completion of diagnostic evaluation (Mayeaux et al., 2017).

In Canada, the Cervical Cancer Prevention and Control Network (CCPCN) has developed a set of pan-Canadian performance indicators to inform the performance monitoring of provincial and territorial cervical cancer screening programmes (PHAC, 2009). The programme performance indicators encompass the following domains: coverage, cytology performance, system capacity, follow-up, and outcomes. The CCPCN has also recommended 10 colposcopy quality indicators, ranging from referral rates and participation to operating room treatment rates (Decker et al., 2019).

(c)   South-East Asia

Although countries in the WHO South-East Asian Region have poor access to cervical cancer screening and treatment services, the WHO Regional Office for South-East Asia and its Member States have compiled a strategic framework for comprehensive control of cervical cancer with training packages for health-care workers on screen-and-treat approaches (WHO/SEARO, 2015).

(d)   Other regions

Cervical cancer screening programmes with integrated quality assurance frameworks exist in Australia (Government of Australia, 2018) and New Zealand (National Screening Unit New Zealand, 2005).

As of 2017, the national cervical cancer screening programme has been implemented in eight of 12 regions of Morocco, where women are screened opportunistically. The current programme has a technical committee responsible for implementation and monitoring. Areas needing improvement have been noted to be: an organized identification and invitation mechanism for the target population; availability of histopathology and treatment facilities for retaining patients at follow-up; improved health-care provider training; and effective data collection and health information systems

with appropriate linkages for quality assurance, monitoring, and evaluation (Selmouni et al., 2019). These findings from Morocco highlight the challenges faced in establishing cervical cancer prevention programmes in LMICs.

References

Adepoju EG, Ilori T, Olowookere SA, Idowu A (2016). Targeting women with free cervical cancer screening: challenges and lessons learnt from Osun state, south-west Nigeria. *Pan Afr Med J*. 24:319. doi:10.11604/pamj.2016.24.319.9300 PMID:28154674

ADS CCI, CDC (2009). Encuesta Nacional de Salud Familiar, FESAL 2008. El Salvador: Asociación Demográfica Salvadoreña, Comité Consultivo Interinstitucional. Atlanta (GA), USA: Centros para el Control y Prevención de Enfermedades. [in Spanish] Available from: https://www.sica.int/busqueda/busqueda_archivo.aspx?Archivo=odoc_79244_1_01072013.pdf.

AIHW (2019). Cervical screening in Australia 2019. Cancer series no. 123. Canberra, Australia: Australian Institute of Health and Welfare. Available from: https://www.aihw.gov.au/reports/cancer-screening/cervical-screening-in-australia-2019/.

Aimagambetova G, Chan CK, Ukybassova T, Imankulova B, Balykov A, Kongrtay K, et al. (2021). Cervical cancer screening and prevention in Kazakhstan and Central Asia. *J Med Screen*. 28(1):48–50. doi:10.1177/0969141320902482 PMID:31980007

Al-Meer FM, Aseel MT, Al-Khalaf J, Al-Kuwari MG, Ismail MFS (2011). Knowledge, attitude and practices regarding cervical cancer and screening among women visiting primary health care in Qatar. *East Mediterr Health J*. 17(11):855–61. doi:10.26719/2011.17.11.856 PMID:22276494

Al-Othman S, Haoudi A, Alhomoud S, Alkhenizan A, Khoja T, Al-Zahrani A (2015). Tackling cancer control in the Gulf Cooperation Council countries. *Lancet Oncol*. 16(5):e246–57. doi:10.1016/S1470-2045(15)70034-3 PMID:25943069

Al Sairafi M, Mohamed FA (2009). Knowledge, attitudes, and practice related to cervical cancer screening among Kuwaiti women. *Med Princ Pract*. 18(1):35–42. doi:10.1159/000163044 PMID:19060489

Altobelli E, Rapacchietta L, Profeta VF, Fagnano R (2019). HPV-vaccination and cancer cervical screening in 53 WHO European countries: an update on prevention programs according to income level. *Cancer Med*. 8(5):2524–34. doi:10.1002/cam4.2048 PMID:30993902

American Cancer Society (2020). Early detection, diagnosis, and staging. Survival rates for cervical cancer [updated 3 January 2020]. Atlanta (GA), USA: American Cancer Society. Available from: https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/survival.html.

American Cancer Society (2021). Cervical cancer prevention and screening: financial issues. Atlanta (GA), USA: American Cancer Society. Available from: https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/prevention-screening-financial-issues.html.

American College of Obstetricians and Gynecologists (2016). Practice Bulletin No. 168: cervical cancer screening and prevention. Obstet Gynecol. 128(4):e111–e130. doi:10.1097/aog.0000000000001708 PMID:27644614

Aminisani N, Fattahpour R, Abedi L, Shamshirgaran SM (2016). Determinants of cervical cancer screening uptake in Kurdish women living in western Iran, 2014. Asian Pac J Cancer Prev. 17(8):3763–7. PMID:27644614

Anderson J, Wysong M, Estep D, Besana G, Kibwana S, Varallo J, et al. (2015). Evaluation of cervical cancer screening programs in Côte d'Ivoire, Guyana, and Tanzania: effect of HIV status. PLoS One. 10(9):e0139242. doi:10.1371/journal.pone.0139242 PMID:26405784

Anorlu RI, Abdul-Kareem FB, Abudu OO, Oyekan TO (2003). Cervical cytology in an urban population in Lagos, Nigeria. J Obstet Gynaecol. 23(3):285–8. doi:10.1080/01443610310000100114 PMID:12850863

Anttila A, Arbyn M, De Vuyst H, Dillner J, Dillner L, Franceschi S, et al., editors (2015). European guidelines for quality assurance in cervical cancer screening. Second edition. Supplements. Luxembourg: Publications Office of the European Union. Available from: https://op.europa.eu/fr/publication-detail/-/publication/a41a4c40-0626-4556-af5b-2619dd1d5ddc.

Araújo ES, Barbosa FM, Ázara CZS, Ferreira TXAM, Tavares SBdN, Amaral RG (2014). Follow-up evaluation of women with abnormal cytopathological tests according to the procedures recommended by the Ministry of Health of Brazil in Goiania city, State of Goias. [in Portuguese] Rev Bras Cancerol. 60(1):7–13.

Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al., editors (2008). European guidelines for quality assurance in cervical cancer screening. Second edition. Luxembourg: Office for Official Publications of the European Communities. Available from: https://op.europa.eu/fr/publication-detail/-/publication/f6d9b1fb-6404-49f2-a4ae-8763ee8b0c52/language-fr/format-PDF/source-search.

Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. (2010). European guidelines for quality assurance in cervical cancer screening. Second edition – summary document. Ann Oncol. 21(3):448–58. doi:10.1093/annonc/mdp471 PMID:20176693

Arbyn M, Rebolj M, De Kok IM, Fender M, Becker N, O'Reilly M, et al. (2009). The challenges of organising cervical screening programmes in the 15 old member states of the European Union. Eur J Cancer. 45(15):2671–8. doi:10.1016/j.ejca.2009.07.016 PMID:19695867

Arrossi S, Paolino M, Laudi R, Gago J, Campanera A, Marín O, et al. (2019). Programmatic human papillomavirus testing in cervical cancer prevention in the Jujuy Demonstration Project in Argentina: a population-based, before-and-after retrospective cohort study. Lancet Glob Health. 7(6):e772–83. doi:10.1016/S2214-109X(19)30048-8 PMID:31097279

Arrossi S, Thouyaret L, Paul L (2015). Prevención del cáncer cervicouterino. Recomendaciones para el tamizaje, seguimiento y tratamiento de mujeres en el marco de programas de tamizaje basados en el test de VPH: actualización 2015. Ciudad Autónoma de Buenos Aires, Argentina: Instituto Nacional del Cáncer Argentina. [in Spanish] Available from: http://repositorio.cedes.org/bitstream/123456789/4318/1/PNPCC_Manual_de_recomendaciones.pdf.

Assoumou SZ, Mabika BM, Mbiguino AN, Mouallif M, Khattabi A, Ennaji MM (2015). Awareness and knowledge regarding of cervical cancer, Pap smear screening and human papillomavirus infection in Gabonese women. BMC Womens Health. 15(1):37. doi:10.1186/s12905-015-0193-2 PMID:25924940

Austad K, Chary A, Xocop SM, Messmer S, King N, Carlson L, et al. (2018). Barriers to cervical cancer screening and the cervical cancer care continuum in rural Guatemala: a mixed-method analysis. J Glob Oncol. 4(4):1–10. doi:10.1200/JGO.17.00228 PMID:30084698

Badrinath P, Ghazal-Aswad S, Osman N, Deemas E, McIlvenny S (2004). A study of knowledge, attitude, and practice of cervical screening among female primary care physicians in the United Arab Emirates. Health Care Women Int. 25(7):663–70. doi:10.1080/07399330490458079 PMID:15487484

Bahamas Ministry of Health (2011). Gynaecology services. Available from: http://www.bahamas.gov.bs/wps/portal/public/Health%20Women/Gynecology/!ut/p/b1/vZTJbqNAEIafJQ_g0GwGjpjNLE2z23BBOOyGgAFjw9OHaEaaUzKXmVSfqvSpv_qlVmMRdsai92SuimSquvek-eyjfUwqCNoCxUJ2T3FAxT1TFSWLVEgcO2HnY7hwwqg-ZCnKn25QLxLuJWuv25e72jGuQaO3tr44GnBFwIREao00SRmCU7uX1vS5UT0KzJmm06psaq0U9bmy2pgD3l2P5scpOFtJR3tUetSbGsqTckV5a_LCnQvOLdjx1x3TukLko7rlkpInhiGYUJKAvPH96oYSDjUB3xnGQZ5HKnazcOWKl5ctWLgFA18UD_6eO_qFAAXy_IYgwvtEBHyv-zRgReo38I3CPHZthoUbxnx5zwFgHnYG2-b10qvdXXq1THgYEIXgBVI4Dn6q2t6MnQnhEPxRGyzxRT

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ba0S/dl4/d5/L2dBISEvZ0FBIS9nQSEh/.

Barchuk A, Bespalov A, Huhtala H, Chimed T, Laricheva I, Belyaev A, et al. (2018). Breast and cervical cancer incidence and mortality trends in Russia 1980–2013. *Cancer Epidemiol*. 55:73–80. doi:10.1016/j.canep.2018.05.008 PMID:29843073

Barrios Fernández AC, Barán Wasilchuk MT, Sosa Argüello LM, Alvarenga Ibáñez JC, Moldano de Campagne NE (2015). Manual nacional de normas y procedimientos para la prevención y el control del cáncer del tracto genital inferior femenino. Asunción, Paraguay: Ministerio de Salud Pública y Bienestar Social de Paraguay [in Spanish] Available from: https://www.iccp-portal.org/system/files/resources/Manual%20de%20Normas%20y%20Procedimientos%20para%20la%20prevencion%20y%20tratamiento%20del%20Cancer%20de%20tracto%20genital%20inferior%20femenino.pdf.

Basu P, Lucas E, Carvalho AL, Sauvaget C, Muwonge R, Herrero R, et al. (2019). Cancer screening in five continents. Lyon, France: International Agency for Research on Cancer. Available from: https://canscreen5.iarc.fr.

Basu P, Majid M (2008). Cervical cancer screening program of Bangladesh: evaluation and formulation of quality assurance standards and guidelines. Bangladesh: United Nations Population Fund (UNFPA). Available from: http://web2.unfpa.org/public/about/oversight/evaluations/docDownload.unfpa?docId=15.

Basu P, Nessa A, Majid M, Rahman JN, Ahmed T (2010). Evaluation of the national cervical cancer screening programme of Bangladesh and the formulation of quality assurance guidelines. *J Fam Plann Reprod Health Care*. 36(3):131–4. doi:10.1783/147118910791749218 PMID:20659365

Basu P, Ponti A, Anttila A, Ronco G, Senore C, Vale DB, et al. (2018). Status of implementation and organization of cancer screening in the European Union Member States – summary results from the second European screening report. *Int J Cancer*. 142(1):44–56. doi:10.1002/ijc.31043 PMID:28940326

Baussano I, Tshomo U, Clifford GM, Tenet V, Tshokey T, Franceschi S (2014). Cervical cancer screening program in Thimphu, Bhutan: population coverage and characteristics associated with screening attendance. *BMC Womens Health*. 14(1):147. doi:10.1186/s12905-014-0147-0 PMID:25433538

Ben Aissa R, Bennour R, Ben Hamida A, Kammoun N, Mansour H, Mhamdi A, et al. (2002). Cervical cancer screening by Pap smear: experience of the national research center in reproductive health. ONFP. [in French] *Tunis Med*. 80(4):203–6. PMID:12416356

Benski AC, Viviano M, Jinoro J, Alec M, Catarino R, Herniainasolo J, et al. (2019). HPV self-testing for primary cervical cancer screening in Madagascar: VIA/VILI triage compliance in HPV-positive women. *PLoS One*. 14(8):e0220632. doi:10.1371/journal.pone.0220632 PMID:31408474

Bigaard J, Hariri J, Lynge E (2000). Cervical cancer screening in Denmark. *Eur J Cancer*. 36(17):2198–204. doi:10.1016/S0959-8049(00)00309-9 PMID:11072204

Binagwaho A, Ngabo F, Wagner CM, Mugeni C, Gatera M, Nutt CT, et al. (2013). Integration of comprehensive women's health programmes into health systems: cervical cancer prevention, care and control in Rwanda. *Bull World Health Organ*. 91(9):697–703. doi:10.2471/BLT.12.116087 PMID:24101786

Bonet Gorbea M, Varona Pérez P (2014). III Encuesta nacional de factores de riesgo y actividades preventivas de enfermedades no transmisibles. Cuba 2010–2011. La Habana, Cuba: Editorial Ciencias Médicas; [in Spanish].

Bovet P, Gédéon J, Louange M, Durasnel P, Aubry P, Gaüzère BA (2013). Health situation and issues in the Seychelles in 2012. [in French] *Med Sante Trop*. 23(3):256–66. doi:10.1684/mst.2013.0222 PMID:24103919

BPJS Kesehatan (2014). Do not worry BPJS ensuring cervical cancer detection before the attack. Jakarta, Indonesia: Badan Penyelenggara Jaminan Sosial Kesehatan. Available from: https://bpjs-kesehatan.go.id/bpjs/index.php/post/read/2014/262/Jangan-Khawatir-BPJS-Kesehatan-Menjamin-Deteksi-Sebelum-Kanker-Serviks-Menyerang/berita?&per_page=36.

Brandão M, Tulsidás S, Damasceno A, Silva-Matos C, Carrilho C, Lunet N (2019). Cervical cancer screening uptake in women aged between 15 and 64 years in Mozambique. *Eur J Cancer Prev*. 28(4):338–43. doi:10.1097/CEJ.0000000000000459 PMID:30020115

Broquet C, Triboullier D, Untiet S, Schafer S, Petignat P, Vassilakos P (2015). Acceptability of self-collected vaginal samples for HPV testing in an urban and rural population of Madagascar. *Afr Health Sci*. 15(3):755–61. doi:10.4314/ahs.v15i3.8 PMID:26957962

Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. (2019a). Human papillomavirus and related diseases in Africa. Summary report. Barcelona, Spain: ICO/IARC Information Centre on HPV and Cancer. Available from: https://www.hpvcentre.net/statistics/reports/XFX.pdf.

Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. (2019b). Human papillomavirus and related diseases in Asia. Summary report. Barcelona, Spain:

ICO/IARC Information Centre on HPV and Cancer. Available from: https://hpvcentre.net/statistics/reports/.

Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. (2019c). Human papillomavirus and related diseases in the Americas. Summary report. Barcelona, Spain: ICO/IARC Information Centre on HPV and Cancer. Available from: https://hpvcentre.net/statistics/reports/.

Burton-Jeangros C, Cullati S, Manor O, Courvoisier DS, Bouchardy C, Guessous I (2017). Cervical cancer screening in Switzerland: cross-sectional trends (1992–2012) in social inequalities. *Eur J Public Health*. 27(1):167–73. doi:10.1093/eurpub/ckw113 PMID:28177486

CADTH (2019). HPV testing for primary cervical cancer screening: recommendations report. CADTH optimal use report no. 7.1c. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK543306/.

Canadian Partnership Against Cancer (2016). Cervical cancer screening in Canada: monitoring and evaluation of quality indicators. Special feature: cervical cancer screening in young women. Results report: January 2011 to December 2013. Toronto, Canada: Canadian Partnership Against Cancer. Available from: https://www.partnershipagainstcancer.ca/wp-content/uploads/2019/01/Cervical-Cancer-Screen-Quality-Indicators-Report-2016-EN.pdf.

Canadian Partnership Against Cancer (2018). Cervical cancer screening in Canada: environmental scan. Toronto, Canada: Canadian Partnership Against Cancer. Available from: https://www.partnershipagainstcancer.ca/topics/cervical-cancer-screening-environmental-scan-2018/.

Canadian Partnership Against Cancer (2019). Canadian strategy for cancer control 2019–2029. Toronto, Canada: Canadian Partnership Against Cancer. Available from: https://www.partnershipagainstcancer.ca/cancer-strategy/.

Canadian Partnership Against Cancer (2020). About us. Toronto, Canada: Canadian Partnership Against Cancer. Available from: https://www.partnershipagainstcancer.ca/about-us/.

Canadian Strategy for Cancer Control (2006). The Canadian Strategy for Cancer Control: a cancer plan for Canada. Discussion paper. Toronto, Canada: Canadian Strategy for Cancer Control. Available from: https://www.partnershipagainstcancer.ca/wp-content/uploads/2015/03/The-Canadian-Strategy-for-Cancer-Control-A-Cancer-Plan-for-Canada_accessible.pdf.

Canadian Task Force on Preventive Health Care (2019). About us. Available from: https://canadiantaskforce.ca/about.

Cancer Council Australia (2018). Medical Services Advisory Committee recommendations for HPV testing. Available from: https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening/Medical_Services_Advisory_Committee_recommendations_for_HPV_testing.

Centers for Disease Control and Prevention (2015). BRFSS prevalence & trends data. Topic: Pap test. Atlanta (GA), USA: Centers for Disease Control and Prevention. Available from: https://nccd.cdc.gov/BRFSSPrevalence/rdPage.aspx?rdReport=DPH_BRFSS.ExploreByTopic&irbLocationType=StatesAndMMSA&islClass=CLASS18&islTopic=TOPIC42&islYear=2018&rdRnd=29096.

Centers for Disease Control and Prevention (2019). National Breast and Cervical Cancer Early Detection Program (NBCCEDP). About the program. Atlanta (GA), USA: Division of Cancer Prevention and Control, Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/cancer/nbccedp/about.htm.

Centers for Disease Control and Prevention, National Center for Health Statistics (2020). National Health Interview Survey. Available from: https://www.cdc.gov/nchs/nhis/index.htm.

Centre for Health Protection (2004). Topical health report no. 4. Prevention and screening of cervical cancer. Hong Kong Special Administrative Region: Surveillance and Epidemiology Branch, Centre for Health Protection, Department of Health. Available from: https://www.chp.gov.hk/files/pdf/grp-thr-report4-en-20041209.pdf.

Centre for Health Protection (2017). Report of population health survey 2014/2015. Hong Kong Special Administrative Region: Centre for Health Protection, Department of Health. Available from: https://www.chp.gov.hk/en/static/51256.html.

Centre for Health Protection (2019). Cervical cancer prevention and screening. Hong Kong Special Administrative Region: Non-communicable Disease Branch, Centre for Health Protection, Department of Health. Available from: https://www.chp.gov.hk/files/pdf/2_cervical_cancer_prevention_and_screening_eng.pdf.

CEPEP (2009). Encuesta Nacional de Demografía y Salud Sexual y Reproductiva 2008, ENDSSR 2008: informe final. Asunción, Paraguay: Centro Paraguayo de Estudios de Población. [in Spanish] Available from: https://pdf.usaid.gov/pdf_docs/PNADR811.pdf.

CESDEM & ICF International (2014). Encuesta Demográfica y de Salud, República Dominicana 2013. Santo Domingo, República Dominicana: Centro de Estudios Sociales y Demográficos. Rockville (MD), USA: ICF International. [in Spanish] Available from: https://repositorio.msp.gob.do/bitstream/

handle/123456789/77/Encuestademsalud2013. pdf?sequence=1&isAllowed=y.

Chen CJ, You SL, Lin LH, Hsu WL, Yang YW (2002). Cancer epidemiology and control in Taiwan: a brief review. *Jpn J Clin Oncol*. 32(Suppl 1):S66–81. doi:10.1093/jjco/hye138 PMID:11959880

Chigbu CO, Onyebuchi AK, Nnakenyi EF, Egbuji CC (2017). Impact of visual inspection with acetic acid plus cryotherapy "see and treat" approach on the reduction of the population burden of cervical preinvasive lesions in Southeast Nigeria. *Niger J Clin Pract*. 20(2):239–43. doi:10.4103/1119-3077.187315 PMID:28091444

Chocontá-Piraquive LA, Alvis-Guzman N, De la Hoz-Restrepo F (2010). How protective is cervical cancer screening against cervical cancer mortality in developing countries? The Colombian case. *BMC Health Serv Res*. 10(1):270. doi:10.1186/1472-6963-10-270 PMID:20846446

Chrysostomou AC, Stylianou DC, Constantinidou A, Kostrikis LG (2018). Cervical cancer screening programs in Europe: the transition towards HPV vaccination and population-based HPV testing. *Viruses*. 10(12):729. doi:10.3390/v10120729 PMID:30572620

CIEE (2019). Encuesta Nacional de Salud y Nutrición, ENSANUT 2018. Cuernavaca Morelos, Mexico: Centro de Investigación en Evaluación y Encuestas, Instituto Nacional de Salud Pública, Secretaría de Salud. [in Spanish] Available from: https://ensanut.insp.mx/encuestas/ensanut2018/index.php.

CIRC, Ministère de la Santé, Fondation Lalla Salma (2017). Programme de dépistage des cancers du sein et du col de l'utérus du Maroc. Etat de la mise en oeuvre, organisation et résultats. [in French] Available from: https://screening.iarc.fr/doc/MorrocoScreeningReport2019. pdf.

CNEGSR (2015). Programa prevención y control del cáncer de la mujer. Ciudad de México, México: Centro Nacional de Equidad de Género y Salud Reproductiva, Gobernio de Mexico. [in Spanish] Available from: https://www.gob.mx/salud/cnegsr/acciones-y-programas/programa-prevencion-y-control-del-cancer-de-la-mujer.

Coleman D, Day N, Douglas G, Farmery E, Lynge E, Philip J, et al. (1993). European guidelines for quality assurance in cervical cancer screening. Europe Against Cancer Programme. *Eur J Cancer*. 29A(Suppl 4):S1–38. PMID:8274301

Cooper CP, Saraiya M (2017). Primary HPV testing recommendations of US providers, 2015. *Prev Med*. 105:372–7. doi:10.1016/j.ypmed.2017.08.006 PMID:29056319

Darj E, Chalise P, Shakya S (2019). Barriers and facilitators to cervical cancer screening in Nepal: a qualitative study. *Sex Reprod Healthc*. 20:20–6. doi:10.1016/j.srhc.2019.02.001 PMID:31084813

Davies P, Dimitrievska V (2015). Situation analysis of cancer breast, cervical and prostate cancer screening in Macedonia. Report for the United Nations Population Fund Macedonia Country Office, 5 May 2015. Macedonia Country Office: United Nations Population Fund.

Decker K, Baines N, Muzyka C, Lee M, Mayrand MH, Yang H, et al. (2019). Measuring colposcopy quality in Canada: development of population-based indicators. *Curr Oncol*. 26(3):e286–91. doi:10.3747/co.26.4709 PMID:31285670

DeGregorio G, Manga S, Kiyang E, Manjuh F, Bradford L, Cholli P, et al. (2017). Implementing a fee-for-service cervical cancer screening and treatment program in Cameroon: challenges and opportunities. *Oncologist*. 22(7):850–9. doi:10.1634/theoncologist.2016-0383 PMID:28536303

Department of Medical Services Thailand (2019). National cervical cancer screening: 15 years experiences of Thailand. Talard-Kwan Nonthaburi, Thailand: Ministry of Public Health. Bangkok, Thailand: National Cancer Institute Thailand.

Dhendup T, Tshering P (2014). Cervical cancer knowledge and screening behaviors among female university graduates of year 2012 attending national graduate orientation program, Bhutan. *BMC Womens Health*. 14(1):44. doi:10.1186/1472-6874-14-44 PMID:24618416

Di J (2017). Opportunities and challenges in cervical cancer screening program in China: SWOT analysis for implementation of program. *Qual Prim Care*. 25(5):282–8. Available from: https://primarycare.imedpub.com/opportunities-and-challenges-in-cervical-cancerscreening-program-in-china-swot-analysis-forimplementation-of-program. php?aid=20761.

Dickinson J, Tsakonas E, Conner Gorber S, Lewin G, Shaw E, Singh H, et al.; Canadian Task Force on Preventive Health Care (2013). Recommendations on screening for cervical cancer. *CMAJ*. 185(1):35–45. doi:10.1503/cmaj.121505 PMID:23297138

Domingo EJ, Dy Echo AV (2009). Epidemiology, prevention and treatment of cervical cancer in the Philippines. *J Gynecol Oncol*. 20(1):11–6. doi:10.3802/jgo.2009.20.1.11 PMID:19471671

Dumont A, Bessières N, Razafindrafara G, Ravit M, Benbassa A (2019). Use of human papilloma virus testing in primary cervical cancer screening in rural Madagascar. [in French] *Rev Epidemiol Sante Publique*. 67(2):120–5. doi:10.1016/j.respe.2018.10.003 PMID:30448093

Elfström KM, Arnheim-Dahlström L, von Karsa L, Dillner J (2015). Cervical cancer screening in Europe: quality assurance and organisation of programmes. *Eur J Cancer*. 51(8):950–68. doi:10.1016/j.ejca.2015.03.008 PMID:25817010

Espinosa V, Cornejo F, Belén Morán M, Calle J, Guevara C (2017). Estrategia nacional para la atención integral del cáncer en el Ecuador. Quito, Ecuador: Ministerio de Salud Pública del Ecuador. [in Spanish] Available from: https://aplicaciones.msp.gob.ec/salud/archivosdigitales/documentosDirecciones/dnn/archivos/ac_0059_2017.pdf.

Farshbaf-Khalili A, Salehi-Pourmehr H, Shahnazi M, Yaghoubi S, Gahremani-Nasab P (2015). Cervical cancer screening in women referred to healthcare centres in Tabriz, Iran. *Niger Med J*. 56(1):28–34. doi:10.4103/0300-1652.149167 PMID:25657490

Fondation Sylvia Bongo Ondimba, Ministère de la Santé gabonais (2014). Guide de bonnes pratiques. Détection précoce des cancers du sein et du col utérin. [in French] Available from: http://www.sylviabongoondimba.org/news/publication-du-premier-guide-de-d%C3%A9tection-pr%C3%A9coce-des-cancers-du-sein-et-du-col-ut%C3%A9rin.

Freire WB, Belmont P, Rivas-Mariño G, Larrea A, Ramírez-Luzuriaga MJ, Silva-Jaramillo KM, et al. (2015). Tomo II: Encuesta Nacional de Salud y Nutrición. Salud Sexual y Reproductiva. ENSANUT-ECU 2012. Quito, Ecuador: Ministerio de Salud Pública, Instituto Nacional de Estadística y Censos. [in Spanish] Available from: https://www.unicef.org/ecuador/media/1761/file/Encuesta%20Nacional%20de%20Salud%20y%20Nutrici%C3%B3n:%20Salud%20Sexual%20y%20Reproductiva.pdf.

French Government (2020). Arrêté du 30 juillet 2020 modifiant l'arrêté du 29 septembre 2006 relatif aux programmes de dépistage organisé des cancers et relatif à l'organisation du dépistage organisé du cancer du col de l'utérus. Journal officiel de la République française. 15 août 2020. [in French] Available from: https://www.legifrance.gouv.fr/download/file/wApphLOCTCpq4PIbCpuUReDH88V2_zW0rTU0Ov0dQlU=/JOE_TEXTE.

Frenk J, Gómez-Dantés O (2018). Health systems in Latin America: the search for universal health coverage. *Arch Med Res*. 49(2):79–83. doi:10.1016/j.arcmed.2018.06.002 PMID:29960828

Gabrielli S, Maggioni E, Fieschi L (2018). Cervical cancer prevention in Senegal: an international cooperation project report. *Acta Biomed*. 89(6-S):29–34. doi:10.23750/abm.v89i6-s.7460 PMID:30038201

Gamage D (2017). Cervical cancer: preventable deaths of women to shape up the future. *JCCPSL*. 23(4):102–8. doi:10.4038/jccpsl.v23i4.8133

George W. Bush Presidential Center (2017). Bush Center annual report 2017. Available from: https://www.bushcenter.org/reports/2017-annual-report/.

Giedion U, Bitrán R, Tristao I, editors (2014). Health benefit plans in Latin America: a regional comparison. Washington (DC), USA: Inter-American Development Bank, Social Protection and Health Division. Available from: https://publications.iadb.org/publications/english/document/Health-Benefit-Plans-in-Latin-America-A-Regional-Comparison.pdf.

Giordano L, Bisanti L, Salamina G, Ancelle Park R, Sancho-Garnier H, Espinas J, et al.; Euromed Cancer working group (2016). The EUROMED CANCER network: state-of-art of cancer screening programmes in non-EU Mediterranean countries. *Eur J Public Health*. 26(1):83–9. doi:10.1093/eurpub/ckv107 PMID:26072520

Global Giving (2021). NNCTR cervical and breast cancer screening activities in Nepal. Sanford (NC), USA: Global Giving. Available from: https://www.globalgiving.org/pfil/6686/projdoc.pdf.

Go Further (2019). Ending AIDS and cervical cancer. Factsheet. Available from: https://gwbcenter.imgix.net/Explore_Our_Work/Taking_Action/GoFurther/go-further-factsheet-2019-02.pdf.

Go Further (2020a). Overview. A partnership that is going further for women. Available from: https://gwbcenter.imgix.net/Publications/Resources/go-further-overview-2020.pdf.

Go Further (2020b). Global highlights. Available from: https://gwbcenter.imgix.net/Publications/Resources/GoFurther_GlobalHighlights_v2.pdf.

Go Further (2020c). Go Further factsheet. Available from: https://gwbcenter.imgix.net/Explore_Our_Work/Taking_Action/GoFurther/go-further-fact-sheet-summer2020.pdf.

Goding Sauer A, Bandi P, Saslow D, Islami F, Jemal A, Fedewa SA (2020). Geographic and sociodemographic differences in cervical cancer screening modalities. *Prev Med*. 133:106014. doi:10.1016/j.ypmed.2020.106014 PMID:32027912

Government of Australia (2018). National Cervical Screening Program – quality framework. Available from: https://www.health.gov.au/resources/publications/national-cervical-screening-program-quality-framework.

Government of Brunei Darussalam (2020). Cervical cancer screening. Available from: http://www.ppkk.gov.bn/SitePages/Cervical-Cancer.aspx.

Government of Canada (2019). Canada's health care system. Ottawa, Canada: Government of Canada. Available from: https://www.canada.ca/en/health-canada/services/health-care-system/reports-publications/health-care-system/canada.html#a9.

Government of Singapore (2020). Preventive health screening statistics. Available from: https://data.gov.sg/dataset/preventive-health-screening-statistics?view_id=e407f7a8-7356-4479-af75-208540947607&resource_id=b011c120-589f-44f4-94bb-1390091b1b71.

Gray JAM, Patnick J, Blanks RG (2008). Maximising benefit and minimising harm of screening. *BMJ*. 336(7642):480–3. doi:10.1136/bmj.39470.643218.94 PMID:18310003

Grover S, Raesima M, Bvochora-Nsingo M, Chiyapo SP, Balang D, Tapela N, et al. (2015). Cervical cancer in Botswana: current state and future steps for screening and treatment programs. *Front Oncol*. 5:239. doi:10.3389/fonc.2015.00239 PMID:26579491

Gultekin M, Karaca MZ, Kucukyildiz I, Dundar S, Keskinkilic B, Turkyilmaz M (2019). Mega HPV laboratories for cervical cancer control: challenges and recommendations from a case study of Turkey. *Papillomavirus Res*. 7:118–22. doi:10.1016/j.pvr.2019.03.002 PMID:30878532

Gultekin M, Zayifoglu Karaca M, Kucukyildiz I, Dundar S, Boztas G, Semra Turan H, et al. (2018). Initial results of population based cervical cancer screening program using HPV testing in one million Turkish women. *Int J Cancer*. 142(9):1952–8. doi:10.1002/ijc.31212 PMID:29235108

Habbema D, De Kok IM, Brown ML (2012). Cervical cancer screening in the United States and the Netherlands: a tale of two countries. *Milbank Q*. 90(1):5–37. doi:10.1111/j.1468-0009.2011.00652.x PMID:22428690

Halahleh K, Gale RP (2018). Cancer care in the Palestinian territories. *Lancet Oncol*. 19(7):e359–64. doi:10.1016/S1470-2045(18)30323-1 PMID:30084383

Hamashima C (2018). Cancer screening guidelines and policy making: 15 years of experience in cancer screening guideline development in Japan. *Jpn J Clin Oncol*. 48(3):278–86. doi:10.1093/jjco/hyx190 PMID:29315389

Haute Autorité de Santé (2019). Public health guidelines summary. Evaluation of human papillomavirus (HPV) tests for primary screening of precancerous and cancerous lesions of the cervix and the role of p16/Ki67 dual immunostaining. Saint-Denis La Plaine, France: Haute Autorité de Santé. Available from: https://www.has-sante.fr/jcms/c_2806160/en/evaluation-of-human-papillomavirus-hpv-tests-for-primary-screening-of-precancerous-and-cancerous-lesions-of-the-cervix-and-the-role-of-p16/ki67-dual-immunostaining.

Hav M, Eav S, Heang N, Pich P, Lim D, Leang V, et al. (2016). Prevalence of Abnormal Cervical Cytology in HIVNegative Women Participating in a Cervical Cancer Screening Program in Calmette Hospital, Cambodia. *Asian Pac J Cancer Prev*. 17(7):3101–3. PMID:27509936

Hernández Villafuerte K, Sáenz Vega I (2006). Primera Encuesta Nacional de Salud en Costa Rica (ENSA 2006): informe técnico y primeros resultados. [in Spanish] Available from: https://ccp.ucr.ac.cr/farmacoeconomia/documentos/ENSA/informetecnicoyprimerosresultadosENSA.pdf.

Hillemanns P, Friese K, Dannecker C, Klug S, Seifert U, Iftner T, et al. (2019). Prevention of cervical cancer: guideline of the DGGG and the DKG (S3 Level, AWMF register number 015/027OL, December 2017) – Part 1 with introduction, screening and the pathology of cervical dysplasia. *Geburtshilfe Frauenheilkd*. 79(2):148–59. doi:10.1055/a-0818-5440 PMID:30792545

Hirth JM, Tan A, Wilkinson GS, Berenson AB (2013). Compliance with cervical cancer screening and human papillomavirus testing guidelines among insured young women. *Am J Obstet Gynecol*. 209(3):200.e1–7. doi:10.1016/j.ajog.2013.05.058 PMID:23727519

Hong S, Lee YY, Lee J, Kim Y, Choi KS, Jun JK, et al. (2020). Trends in cancer screening rates among Korean men and women: results of the Korean National Cancer Screening Survey, 2004–2018. *Cancer Res Treat*. doi:10.4143/crt.2020.263 PMID:33091969

HSE (2020). Cervical screening. Health Service Executive. Available from: https://www2.hse.ie/cervical-screening/.

IARC (2005). Cervix cancer screening. *IARC Handb Cancer Prev*. 10:1–302. Available from: http://publications.iarc.fr/380.

ICO/IARC Information Centre on HPV and Cancer (2019). Nepal. Human papillomavirus and related cancers, fact sheet 2018. Available from: https://hpvcentre.net/statistics/reports/NPL_FS.pdf.

IETS (2020). Instituto de Evaluación Tecnologíca en Salud. Bogotá, Colombia. [in Spanish] Available from: https://www.iets.org.co/.

INEI (2014). Perú enfermedades no transmisibles y transmisibles, 2013. Capítulo 2. Programa de prevención y control del cáncer. Lima, Perú: Instituto Nacional de Estadística e Información. [in Spanish] Available from: https://www.inei.gob.pe/media/MenuRecursivo/publicaciones_digitales/Est/Lib1152/index.html.

INIDE & MINSA (2014). Encuesta Nicaragüense de Demografía y Salud, ENDESA 2011/12: informe final. Managua, Nicaragua: Instituto Nacional de Información de Desarrollo, Ministerio de Salud. [in Spanish] Available from: https://nicaragua.unfpa.org/sites/default/files/pub-pdf/ENDESA-2011-12-completa.pdf.

Institute of Medicine (1990). Medicare: a strategy for quality assurance, Volume II: sources and methods. Washington (DC), USA: National Academies Press. doi:10.17226/1548

Institute of Medicine (2001). Envisioning the national health care quality report. Washington (DC), USA: National Academies Press. doi:10.17226/10073

Instituto Mexicano del Seguro Social (2011). Guía de práctica clínica GPC: prevención y detección oportuna del cáncer cérvico uterino en el primer nivel de atención.

[in Spanish] Available from: http://www.imss.gob.mx/sites/all/statics/guiasclinicas/146GER.pdf.

Jin AZ, Louange EC, Chow KY, Fock CWL (2013). Evaluation of the national cervical cancer screening programme in Singapore. *Singapore Med J.* 54(2):96–101. doi:10.11622/smedj.2013032 PMID:23462834

Johnson LG, Ramogola-Masire D, Teitelman AM, Jemmott JB, Buttenheim AM (2020). Assessing nurses' adherence to the see-and-treat guidelines of Botswana's national cervical cancer prevention programme. *Cancer Prev Res (Phila).* 13(3):329–36. doi:10.1158/1940-6207.CAPR-19-0348 PMID:31852663

Jolly PE, Mthethwa-Hleta S, Padilla LA, Pettis J, Winston S, Akinyemiju TF, et al. (2017). Screening, prevalence, and risk factors for cervical lesions among HIV positive and HIV negative women in Swaziland. *BMC Public Health.* 17(1):218. doi:10.1186/s12889-017-4120-3 PMID:28222714

Kahesa C, Kjaer S, Mwaiselage J, Ngoma T, Tersbol B, Dartell M, et al. (2012). Determinants of acceptance of cervical cancer screening in Dar es Salaam, Tanzania. *BMC Public Health.* 12(1):1093. doi:10.1186/1471-2458-12-1093 PMID:23253445

Kanavos P, Colville Parkin G, Kamphuis B, Gill J (2019). Latin America healthcare system overview: a comparative analysis of fiscal space in healthcare. London, UK: London School of Economics and Political Science. Available from: https://www.lse.ac.uk/business/consulting/reports/latin-america-healthcare-system-overview.

Kang L, Qiao R (2014). Cancer screening and prevention in China. *Cancer Contr.* 2014:131–3. Available from: http://cancercontrol.info/wp-content/uploads/2014/08/131-133-Qiao_cc2014.pdf.

Kepka D, Breen N, King JB, Benard VB, Saraiya M (2014). Overuse of Papanicolaou testing among older women and among women without a cervix. *JAMA Intern Med.* 174(2):293–6. doi:10.1001/jamainternmed.2013.12607 PMID:24276745

Khazaee-Pool M, Yargholi F, Jafari F, Ponnet K (2018). Exploring Iranian women's perceptions and experiences regarding cervical cancer-preventive behaviors. *BMC Womens Health.* 18(1):145. doi:10.1186/s12905-018-0635-8 PMID:30170632

Khozaim K, Orang'o E, Christoffersen-Deb A, Itsura P, Oguda J, Muliro H, et al. (2014). Successes and challenges of establishing a cervical cancer screening and treatment program in western Kenya. *Int J Gynaecol Obstet.* 124(1):12–8. doi:10.1016/j.ijgo.2013.06.035 PMID:24140218

Khuhaprema T, Attasara P, Srivatanakul P, Sangrajrang S, Muwonge R, Sauvaget C, et al. (2012). Organization and evolution of organized cervical cytology screening in Thailand. *Int J Gynaecol Obstet.* 118(2):107–11. doi:10.1016/j.ijgo.2012.03.031 PMID:22613493

Kim JJ, Campos NG, Sy S, Burger EA, Cuzick J, Castle PE, et al.; New Mexico HPV Pap Registry Steering Committee (2015). Inefficiencies and high-value improvements in U.S. cervical cancer screening practice: a cost-effectiveness analysis. *Ann Intern Med.* 163(8):589–97. doi:10.7326/M15-0420 PMID:26414147

Kim Y, Jun JK, Choi KS, Lee HY, Park EC (2011). Overview of the national cancer screening programme and the cancer screening status in Korea. *Asian Pac J Cancer Prev.* 12(3):725–30. PMID:21627372

Kim YM, Lambe FM, Soetikno D, Wysong M, Tergas AI, Rajbhandari P, et al. (2013). Evaluation of a 5-year cervical cancer prevention project in Indonesia: opportunities, issues, and challenges. *J Obstet Gynaecol Res.* 39(6):1190–9. doi:10.1111/jog.12052 PMID:23718197

Kiran T, Kopp A, Moineddin R, Glazier RH (2015). Longitudinal evaluation of physician payment reform and team-based care for chronic disease management and prevention. *CMAJ.* 187(17):E494–502. doi:10.1503/cmaj.150579 PMID:26391722

Kumakech E, Andersson S, Wabinga H, Berggren V (2014). Integration of HIV and cervical cancer screening perceptions of healthcare providers and policy makers in Uganda. *BMC Public Health.* 14(1):810. doi:10.1186/1471-2458-14-810 PMID:25099996

Kumara WGN, Dasanayake DLW (2017). Cervical cytology screening: knowledge attitudes and behaviour of public health midwives in an urban district in Sri Lanka. *Sri Lanka J Obstet Gynaecol.* 39(1):16–9. doi:10.4038/sljog.v39i1.7807

Kunckler M, Schumacher F, Kenfack B, Catarino R, Viviano M, Tincho E, et al. (2017). Cervical cancer screening in a low-resource setting: a pilot study on an HPV-based screen-and-treat approach. *Cancer Med.* 6(7):1752–61. doi:10.1002/cam4.1089 PMID:28580596

Lee MY, Telisinghe PU, Ramasamy R (2012). Cervical cancer in Brunei Darussalam. *Singapore Med J.* 53(9):604–7. PMID:23023903

Lee WC, Shin HR, Kim CM (2002). Establishing cancer screening recommendations for major cancers in Korea. *J Korean Med Assoc.* 45(8):959–63. doi:10.5124/jkma.2002.45.8.959

Luciani S, Hutton M, Hennis A, Hassel T (2017). Cancer prevention and control in the Caribbean. *Cancer Contr.* 2017:53–61. Available from: http://www.cancercontrol.info/wp-content/uploads/2017/12/53-61-Lucini-1.pdf.

Macgregor JE, Moss SM, Parkin DM, Day NE (1985). A case-control study of cervical cancer screening in north east Scotland. *Br Med J (Clin Res Ed).* 290(6481):1543–6. doi:10.1136/bmj.290.6481.1543 PMID:3924157

Magnus K, Langmark F, Andersen A (1987). Mass screening for cervical cancer in Ostfold county of Norway 1959–77. *Int J Cancer.* 39(3):311–6. doi:10.1002/ijc.2910390308 PMID:3818122

Makura CBT, Schnippel K, Michelow P, Chibwesha CJ, Goeieman B, Jordaan S, et al. (2016). Choropleth mapping of cervical cancer screening in South Africa using healthcare facility-level data from the national laboratory network. *AIMS Public Health*. 3(4):849–62. doi:10.3934/publichealth.2016.4.849 PMID:29546199

Malawi Ministry of Health and Population (2019). National service delivery guidelines for cervical cancer prevention and control. Available from: http://populationmalawi.org/wp1/wp-content/uploads/2020/02/Malawi_CC_Service_Delivery_Guidelines_FINAL-Print-Ready-Version.pdf.

Maldives UNFPA (2014). Practical and cost-effective screening for cervical cancer using VIA launched in Maldives. Malé, Maldives: United Nations Population Fund (UNFPA). Available from: https://maldives.unfpa.org/en/news/practical-and-cost-effective-screening-cervical-cancer-using-launched-maldives.

Martin D, Miller AP, Quesnel-Vallée A, Caron NR, Vissandjée B, Marchildon GP (2018). Canada's universal health-care system: achieving its potential. *Lancet*. 391(10131):1718–35. doi:10.1016/S0140-6736(18)30181-8 PMID:29483027

Masalu N, Serra P, Amadori D, Kahima J, Majinge C, Rwehabura J, et al. (2017). Setting up a community-based cervical screening service in a low-income country: a pilot study from north-western Tanzania. *Int J Public Health*. 62(7):755–62. doi:10.1007/s00038-017-0971-8 PMID:28424832

Maseko FC, Chirwa ML, Muula AS (2014). Client satisfaction with cervical cancer screening in Malawi. *BMC Health Serv Res*. 14(1):420. doi:10.1186/1472-6963-14-420 PMID:25245860

Maseko FC, Chirwa ML, Muula AS (2015). Health systems challenges in cervical cancer prevention program in Malawi. *Glob Health Action*. 8(1):26282. doi:10.3402/gha.v8.26282 PMID:25623612

Maternal and Child Health Integrated Program (2012). Guyana cervical cancer prevention project: October 1, 2010–September 30, 2012. Baltimore (MD), USA: Jhpiego. Available from: https://www.mchip.net/sites/default/files/MCHIP_Guyana%20Closeout%20Report.pdf.

Maver PJ, Poljak M (2020). Primary HPV-based cervical cancer screening in Europe: implementation status, challenges, and future plans. *Clin Microbiol Infect*. 26(5):579–83. doi:10.1016/j.cmi.2019.09.006 PMID:31539637

Mayeaux EJ Jr, Novetsky AP, Chelmow D, Garcia F, Choma K, Liu AH, et al. (2017). ASCCP colposcopy standards: colposcopy quality improvement recommendations for the United States. *J Low Genit Tract Dis*. 21(4):242–8. doi:10.1097/LGT.0000000000000342 PMID:28953113

Medicaid/CHIP (2019). Quality of care for adults in Medicaid: findings from the 2018 adult core set. Washington (DC), USA: Medicaid. Available from: https://www.medicaid.gov/medicaid/quality-of-care/downloads/performance-measurement/2019-adult-chart-pack.pdf.

Melo A, Vásquez AM, Andana A, Matamala M, Pino T, Guzmán P, et al. (2014). Genotyping of human papillomavirus in women under 25 years old treated in the screening program for cervical cancer. [in Spanish] *Rev Chilena Infectol*. 31(5):542–8. doi:10.4067/S0716-10182014000500005 PMID:25491452

Miles A, Cockburn J, Smith RA, Wardle J (2004). A perspective from countries using organized screening programs. *Cancer*. 101(S5):1201–13. doi:10.1002/cncr.20505 PMID:15316915

Ministère de la Santé Publique Madagascar (2011). Manuel national de normes et procédures pour la prévention du cancer du col utérin. [in French]. Available from: https://extranet.who.int/ncdccs/Data/MDG_NCD_Prevention_Uterine%20cancer.pdf.

Ministère de la Santé Tunisien (2015). Plan pour la lutte contre le cancer en Tunisie 2015–2019. [in French]. Available from: https://www.iccp-portal.org/system/files/plans/Plan_pour_la_lutte_contre_le_cancer_2015-2019_Tunisie.pdf.

Ministério da Saúde de Portugal (2021). Programa Nacional para as Doenças Oncológicas. Avaliação e monitorização dos rastreios oncológicos organizados de base populacional 2019/2020 – Portugal. Lisbon, Portugal: Direção-Geral da Saúde.

Ministério da Saúde do Brasil (2016). Diretrizes brasileiras para o rastreamento do câncer do colo do útero. 2a edição revista, ampliada e atualizada. Rio de Janeiro, Brazil: Ministério da Saúde, Instituto Nacional de Câncer José Alencar Gomes Da Silva. [in Portuguese] Available from: http://www.citologiaclinica.org.br/site/pdf/documentos/diretrizes-para-o-rastreamento-do-cancer-do-colo-do-utero_2016.pdf.

Ministério da Saúde do Brasil (2017). Vigitel Brasil 2016 Saúde Suplementar: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. Rio de Janeiro, Brazil: Ministério da Saúde, Agência Nacional de Saúde Suplementar. [in Portuguese] Available from: https://www.ans.gov.br/images/Vigitel_Saude_Suplementar.pdf.

Ministério da Saúde do Brasil (2020). Rede Brasileira de Avaliação de Tecnologías Sanitarias (REBRATS). [in Portuguese] Available from: https://rebrats.saude.gov.br/.

Ministerio de Desarrollo Social de Chile (2018). Encuesta de Caracterización Socioeconómica Nacional Casen 2017. Síntesis de resultados. Santiago, Chile: Gobierno de Chile. [in Spanish] Available from: http://observatorio.ministeriodesarrollosocial.gob.cl/storage/docs/casen/2017/Resultados_Salud_casen_2017.pdf

Ministerio de Desarrollo Social y Familia de Chile (2018). Encuesta de Caracterización Socioeconómica Nacional Casen 2017. Base de datos. Santiago, Chile: Gobierno de Chile. [in Spanish] Available from: http://observatorio.ministeriodesarrollosocial.gob.cl.

Ministerio de Salud & Caja de Seguro Social de Panamá (2017). Normas de prevención, detección y seguimiento de las lesiones preinvasoras del cuello uterino y guías de manejo. Panama City, Panama: Ministerio de Salud, Caja de Seguro Social, República de Panamá, Coordinación Nacional de Salud Sexual y Reproductiva. [in Spanish] Available from: http://www.minsa.gob.pa/sites/default/files/programas/normas_de_prevencion_cacu.pdf.

Ministerio de Salud de Argentina (2019). Salud publicó el informe completo de la 4a Encuesta Nacional de Factores de Riesgo. Ciudad Autónoma de Buenos Aires, Argentina: Ministerio de Salud de Argentina. [in Spanish] Available from: https://www.argentina.gob.ar/noticias/salud-publico-el-informe-completo-de-la-4deg-encuesta-nacional-de-factores-de-riesgo.

Ministério de Salud de Chile (2015). Guías clínicas AUGE: cáncer cérvico uterino. [in Spanish] Available from: https://www.minsal.cl/wp-content/uploads/2015/09/GPC-CaCU.pdf.

Ministério de Salud de Chile (2017). Evaluación de Tecnologías Sanitarias (ETESA). Santiago, Chile: Ministerio de Salud. [in Spanish] Available from: https://www.minsal.cl/etesa-objetivos/.

Ministerio de Salud de Costa Rica (2006). Decretos No. 33119-S: Normas y procedimientos de atención integral a la mujer para la prevención y manejo del cáncer de cuello de útero, para el I y II nivel de atención y normas de laboratorios de citología. La Gaceta. 131:1–24. [in Spanish] Available from: https://www.imprentanacional.go.cr/pub/2006/07/07/ALCA43_07_07_2006.html.

Ministerio de Salud de Costa Rica (2007). Decretos No. 33650-S: Manual de normas y procedimientos de atención integral a la mujer para la prevención y manejo del cáncer de cuello de útero, para el I-II y III nivel de atención y normas de laboratorios de citología. La Gaceta Digital. 171:1–12. [in Spanish] Available from: https://extranet.who.int/ncdccs/Data/CRI_B5_COR_Poli%cc%81tica_CA_cuellouterino.pdf.

Ministerio de Salud de El Salvador (2015). Lineamientos técnicos para la prevención y control del cáncer cérvico uterino y de mama. San Salvador, El Salvador. [in Spanish] Available from: http://asp.salud.gob.sv/regulacion/pdf/lineamientos/lineamientos_prevencion_cancer_cervico_uterino_y_de_mama_v3.pdf.

Ministerio de Salud de Nicaragua (2010). Protocolo de prevención del cáncer cérvico uterino a través del tamizaje con inspección visual con ácido acético (IVVA) y tratamiento con crioterapia. Normativa – 037. Managua, Nicaragua: Ministerio de Salud. [in Spanish] Available from: https://data.miraquetemiro.org/sites/default/files/documentos/N-037_Prot_prev_cancer-cerv_uter_atraves-tamizaje.6013.pdf.

Ministerio de Salud de Perú (2019). Resolución Ministerial No. 576-2019/MINSA. Directiva sanitaria para la prevención del cáncer de cuello uterino mediante la detección temprana y tratamiento de lesiones pre malignas incluyendo carcinoma in situ. Lima, Perú. [in Spanish] Available from: https://www.gob.pe/institucion/minsa/normas-legales/282080-576-2019-minsa.

Ministerio de Salud Pública de Cuba (2018). Guía de cáncer cervicouterino. Acciones para su control. Available from: https://files.sld.cu/higienepidemiologia/files/2018/12/prog_nac_c%c3%a1ncer_1.pdf.

Ministerio de Salud Pública de Uruguay (2018). 2da encuesta nacional de factores de riesgo de enfermedades no transmisibles. Montevideo, Uruguay: Ministerio de Salud Pública, Programa de Prevención de Enfermedades No Transmisibles (PPENT). [in Spanish] Available from: https://www.gub.uy/ministerio-salud-publica/comunicacion/publicaciones/2da-encuesta-nacional-de-factores-de-riesgo-de-enfermedades-no.

Ministerio de Salud Pública y Asistencia Social de Guatemala (2020). Guía de atención integral para la prevención, detección y tratamiento de lesiones precursoras del cáncer cérvico uterino. Segunda edición. Guatemala City, Guatemala: Ministerio de Salud Pública y Asistencia Social de Guatemala, Programa Nacional de Salud Reproductiva, Departamento de Regulación de los Programas de Atención a las Personas. [in Spanish] Available from: https://osarguatemala.org/guia-de-atencion-integral-para-la-prevencion-deteccion-y-tratamiento-de-lesiones-precursoras-del-cancer-cervico-uterino/.

Ministerio de Salud Pública y Bienestar Social de Paraguay (2017a). El Pap puede salvarte la vida. [in Spanish] Available from: https://www.mspbs.gov.py/portal/11016/el-pap-puede-salvarte-la-vida.html.

Ministerio de Salud Pública y Bienestar Social de Paraguay (2017b). Novedosa tecnología para detección del cáncer de cuello uterino disponible en servicios. [in Spanish] Available from: https://www.mspbs.gov.py/portal/11476/novedosa-tecnologia-para-deteccion-del-cancer-de-cuello-uterino-disponible-en-servicios.html.

Ministerio de Salud y Deportes Bolivia (2009a). Encuesta Nacional de Demografía y Salud ENDSA 2008. La Paz, Bolivia: Ministerio de Salud y Deportes Bolivia, Programa Reforma de Salud, Instituto Nacional de Estadística y Macro International. [in Spanish] Available from: https://bolivia.unfpa.org/sites/default/files/pub-pdf/ENDSA%202008_0.pdf.

Ministerio de Salud y Deportes Bolivia (2009b). Norma nacional, reglas, protocolos y procedimientos para la detección y control de cáncer de cuello uterino. Cuarta edición actualizada. Publicación 121. La Paz, Bolivia: Ministerio de Salud y Deportes Bolivia, Dirección General de Salud, Unidad de Servicios de Salud y Calidad. [in Spanish] Available from: https://www.minsalud.gob.bo/images/Documentacion/redes_salud/NORMA%20NACIONAL%20REGLAS%20PROTOCOLOS%20Y%20PROCEDMIENTOS%20PARA%20LA%20DET.pdf.

Ministerio de Salud y Protección Social de Colombia (2014). Guía de práctica clínica para la detección y manejo de lesiones precancerosas de cuello uterino – guía para profesionales de la salud. Bogotá, Colombia: Minsalud, Instituto Nacional de Cancerología. [in Spanish] Available from: https://medicosgeneralescolombianos.com/sitio/Guias_minsalud/LPC-Guia-profesionales.pdf.

Ministerio de Salud y Protección Social de Colombia (2015). Encuesta Nacional de Demografía y Salud, Colombia. Tomo I. Componente Demográfico. Bogotá, Colombia: Minsalud, Profamilia. [in Spanish] Available from: https://dhsprogram.com/pubs/pdf/FR334/FR334.pdf.

Ministerio de Salud y Protección Social de Colombia (2018). Resolución número 3280 de 2018. Bogotá, Colombia: Minsalud. [in Spanish] Available from: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/resolucion-3280-de-2018.pdf.

Ministerio de Salud y Protección Social de Colombia (2019). Resolución número 276 de 2019. Bogotá, Colombia: Minsalud. [in Spanish] Available from: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/resolucion-276-de-2019.pdf.

Ministry of Community Development, Mother and Child Health Zambia, Ministry of Health Zambia (2015). Visual inspection with acetic acid (VIA) and cryotherapy. A reference manual for trainers and health care providers. Available from: https://www.moh.gov.zm/docs/VIA-CryoReferenceManualZambiaMarch2015.pdf.

Ministry of Health and Family Welfare, Government of India (2016). Operational framework: management of common cancers. Available from: http://cancerindia.org.in/wp-content/uploads/2017/11/Operational_Framework_Management_of_Common_Cancers.pdf.

Ministry of Health and Welfare, Health Promotion Administration (2018). Annual report. Available from: https://www.hpa.gov.tw/Pages/ashx/File.ashx?FilePath=~/File/Attach/10231/File_11648.pdf.

Ministry of Health Belize (2016). Cervical cancer clinical guidelines. Available from: https://www.iccp-portal.org/sites/default/files/resources/CCC_Guidelines_bro_04.compressed%20%282%29.pdf.

Ministry of Health Bhutan (2014). 2012 National Health Survey. Thimphu, Bhutan: Ministry of Health. Available from: http://www.moh.gov.bt/wp-content/uploads/moh-files/nationalHealthSurvey2012.pdf.

Ministry of Health Ghana (2011). National strategy for cancer control in Ghana 2012–2016. Available from: https://www.iccp-portal.org/system/files/plans/Cancer%20Plan%20Ghana%20Ministry%20of%20Health.pdf.

Ministry of Health Guyana (2020). Guyana strategic plan for the integrated prevention and control of chronic non-communicable diseases and their risk factors 2013–2020. Available from: https://www.paho.org/guy/index.php?option=com_docman&view=download&category_slug=not-communicable&alias=119-guyana-ncds-strategic-plan-2013-2020&Itemid=291.

Ministry of Health Indonesia. (2019). Data dan informasi: profil kesehatan Indonesia 2018. Available from: https://pusdatin.kemkes.go.id/resources/download/pusdatin/profil-kesehatan-indonesia/PROFIL_KESEHATAN_2018_1.pdf.

Ministry of Health Jamaica (2011). National guidelines for cervical cancer prevention and control. Available from: https://extranet.who.int/ncdccs/Data/JAM_D1_JAM-Cervical-Cancer-guidelines.pdf.

Ministry of Health, Labour and Welfare Japan (2017). Summary report of comprehensive survey of living conditions 2016. Tokyo, Japan: Ministry of Health, Labour and Welfare. Available from: https://www.mhlw.go.jp/english/database/db-hss/dl/report_gaikyo_2016.pdf.

Ministry of Health Malawi (2018). National cervical cancer strategy 2016–2020, Malawi. Lilongwe, Malawi: United Nations Population Fund. Available from: https://malawi.unfpa.org/sites/default/files/resource-pdf/National_Cervical_Cancer_Strategy_A5_30Oct17_WEB.pdf.

Ministry of Health Malaysia (2019). Guidelines for primary HPV testing in cervical cancer screening in Malaysia. Putrajaya, Malaysia: Family Health Development Division, Ministry of Health Malaysia. Available from: https://www.ogsm.org.my/docs/GUIDELINES%20FOR%20PRIMARY%20HPV%20TESTING%20FOR%20CERVICAL%20CANCER%20SCREENING%20IN%20MALAYSIA.pdf.

Ministry of Health Maldives (2016). National action plan for implementation and strategic plan: National Cervical Cancer Screening Program in Maldives. Available from: http://health.gov.mv/Uploads/Downloads//Informations/Informations(53).pdf.

Ministry of Health New Zealand (2019). Report of the Parliamentary Review Committee regarding the National Cervical Screening Programme. Wellington,

New Zealand: Ministry of Health. Available from: https://www.health.govt.nz/publication/report-parliamentary-review-committee-regarding-national-cervical-screening-programme-april-2019.

Ministry of Health Singapore (2019). Release of new screening test review committee guidelines, including changes to diabetes mellitus, lipid disorders, and cervical cancer screening. MOH circular no. 08/2019. Available from: https://www.moh.gov.sg/docs/librariesprovider5/licensing-terms-and-conditions/moh-cir-no-08_2019_6mar19_screening.pdf.

Ministry of Health Sri Lanka (2014). Annual report on family health 2013. Colombo, Sri Lanka: Family Health Bureau, Ministry of Health. Available from: https://fhb.health.gov.lk/index.php/en/resources/annual-report.

Ministry of Health Sri Lanka (2019). Annual report of the Family Health Bureau 2017. Colombo, Sri Lanka: Family Health Bureau, Ministry of Health. Available from: https://fhb.health.gov.lk/index.php/en/resources/annual-report.

Ministry of Public Health and Sanitation Kenya, Ministry of Medical Services Kenya (2012). National Cervical Cancer Prevention Program: strategic plan 2012–2015. Available from: https://www.iccp-portal.org/system/files/plans/National%20Cervical%20Cancer%20Prevention%20Plan%20FINALFeb%202012.pdf.

Monica MR, Mishra R (2020). An epidemiological study of cervical and breast screening in India: district-level analysis. BMC Womens Health. 20(1):225. doi:10.1186/s12905-020-01083-6 PMID:33028336

Moon TD, Silva-Matos C, Cordoso A, Baptista AJ, Sidat M, Vermund SH (2012). Implementation of cervical cancer screening using visual inspection with acetic acid in rural Mozambique: successes and challenges using HIV care and treatment programme investments in Zambézia Province. J Int AIDS Soc. 15(2):17406. doi:10.7448/IAS.15.2.17406 PMID:22713260

Msyamboza KP, Phiri T, Sichali W, Kwenda W, Kachale F (2016). Cervical cancer screening uptake and challenges in Malawi from 2011 to 2015: retrospective cohort study. BMC Public Health. 16(1):806. doi:10.1186/s12889-016-3530-y PMID:27535359

Muniz S, Briozzo L, Brescia A, Clavell E, Gallo LE, Noble A, et al. (2015). Guía de práctica clínica de tamizaje de cáncer de cuello de útero. Montevideo, Uruguay: Ministerio de Salud Pública de Uruguay. [in Spanish] Available from: https://www.gub.uy/ministerio-salud-publica/sites/ministerio-salud-publica/files/documentos/publicaciones/Guia%20de%20Practica%20clinica%20Cancer%20Cuello%20Uterino%202014.pdf.

Murillo R (2019). Social inequalities in cancer in Latin America. In: Vaccarella S, Lortet-Tieulent J, Saracci R, Conway DI, Straif K, Wild CP, editors. Reducing social inequalities in cancer: evidence and priorities for research (IARC Scientific Publications, No. 168).

Lyon, France: International Agency for Research on Cancer; pp. 223–6. Available from: http://publications.iarc.fr/580.

Murillo R, Almonte M, Pereira A, Ferrer E, Gamboa OA, Jerónimo J, et al. (2008). Cervical cancer screening programs in Latin America and the Caribbean. Vaccine. 26(Suppl 11):L37–48. doi:10.1016/j.vaccine.2008.06.013 PMID:18945401

Murillo R, Herrero R, Sierra MS, Forman D (2016). Cervical cancer in Central and South America: Burden of disease and status of disease control. Cancer Epidemiol. 44(Suppl 1):S121–30. doi:10.1016/j.canep.2016.07.015 PMID:27678314

Muwonge R, Manuel MG, Filipe AP, Dumas JB, Frank MR, Sankaranarayanan R (2010). Visual screening for early detection of cervical neoplasia in Angola. Int J Gynaecol Obstet. 111(1):68–72. doi:10.1016/j.ijgo.2010.04.024 PMID:20570259

Muwonge R, Walter SD, Wesley RS, Basu P, Shastri SS, Thara S, et al.; IARC Multicentre Study Group on Cervical Cancer Early Detection (2007). Assessing the gain in diagnostic performance when two visual inspection methods are combined for cervical cancer prevention. J Med Screen. 14(3):144–50. doi:10.1258/096914107782066158 PMID:17925087

Mwanahamuntu MH, Sahasrabuddhe VV, Kapambwe S, Pfaendler KS, Chibwesha C, Mkumba G, et al. (2011). Advancing cervical cancer prevention initiatives in resource-constrained settings: insights from the Cervical Cancer Prevention Program in Zambia. PLoS Med. 8(5):e1001032. doi:10.1371/journal.pmed.1001032 PMID:21610859

Mwanahamuntu MH, Sahasrabuddhe VV, Pfaendler KS, Mudenda V, Hicks ML, Vermund SH, et al. (2009). Implementation of 'see-and-treat' cervical cancer prevention services linked to HIV care in Zambia. AIDS. 23(6):N1–5. doi:10.1097/QAD.0b013e3283236e11 PMID:19279439

National Department of Health South Africa (2020). Cervical cancer prevention and control policy, South Africa, 2019. Pretoria, South Africa: National Department of Health. Available from: https://cansa.org.za/files/2021/03/cervical_cancer_prevention_and_control_policy.pdf.

National Screening Unit New Zealand (2005). Improving quality: a framework for screening programmes in New Zealand. Available from: https://www.nsu.govt.nz/system/files/resources/quality-framework.pdf.

National Screening Unit New Zealand (2020a). Clinical practice guideline for cervical screening in New Zealand 2020. Available from: https://www.nsu.govt.nz/health-professionals/national-cervical-screening-programme/clinical-practice-guidelines-cervical.

National Screening Unit New Zealand (2020b). HPV primary screening. Available from: https://www.nsu.govt.nz/

health-professionals/national-cervical-screening-programme/hpv-primary-screening.

National Screening Unit New Zealand (2021). National Cervical Screening Programme coverage report. Available from: https://minhealthnz.shinyapps.io/nsu-ncsp-coverage/.

Ndejjo R, Mukama T, Kiguli J, Musoke D (2017). Knowledge, facilitators and barriers to cervical cancer screening among women in Uganda: a qualitative study. *BMJ Open*. 7(6):e016282. doi:10.1136/bmjopen-2017-016282 PMID:28606908

Nessa A, Hussain MA, Rahman JN, Rashid MH, Muwonge R, Sankaranarayanan R (2010). Screening for cervical neoplasia in Bangladesh using visual inspection with acetic acid. *Int J Gynaecol Obstet*. 111(2):115–8. doi:10.1016/j.ijgo.2010.06.004 PMID:20674919

Obel J, McKenzie J, Buenconsejo-Lum LE, Durand AM, Ekeroma A, Souares Y, et al. (2015). Mapping HPV vaccination and cervical cancer screening practice in the Pacific region – strengthening national and regional cervical cancer prevention. *Asian Pac J Cancer Prev*. 16(8):3435–42. doi:10.7314/APJCP.2015.16.8.3435 PMID:25921158

Oluwole D, Kraemer J; Pink Ribbon Red Ribbon (2013). Innovative public-private partnership: a diagonal approach to combating women's cancers in Africa. *Bull World Health Organ*. 91(9):691–6. doi:10.2471/BLT.12.109777 PMID:24101785

Ouedraogo Y, Furlane G, Fruhauf T, Badolo O, Bonkoungou M, Pleah T, et al. (2018). Expanding the single-visit approach for cervical cancer prevention: successes and lessons from Burkina Faso. *Glob Health Sci Pract*. 6(2):288–98. doi:10.9745/GHSP-D-17-00326 PMID:29959272

PAHO (2010). Cervical cancer prevention and control programs: a rapid assessment in 12 countries of Latin America. Washington (DC), USA: Pan American Health Organization. Available from: https://www.paho.org/en/documents/cervical-cancer-prevention-and-control-programs-rapid-assessment-12-countries-latin.

PAHO (2013). Situational analysis of cervical cancer prevention and control in the Caribbean. Washington (DC), USA: Pan American Health Organization. Available from: https://www.paho.org/hq/dmdocuments/2013/Caribbean-cxca-situation-analysis-2013.pdf.

PAHO (2019). Core indicators 2018: health situation in the Americas. Washington (DC), USA: Pan American Health Organization. Available from: https://iris.paho.org/bitstream/handle/10665.2/49511/CoreIndicators2018_eng.pdf.

PAHO (2020a). PAHO countries and centers: subregions. Washington (DC), USA: Pan American Health Organization. Available from: https://www.paho.org/commoninfo/viewsubregion.php?lang=en&idsubregion=0.

PAHO (2020b). Core indicators 2019: health trends in the Americas. Washington (DC), USA: Pan American Health Organization. Available from: https://iris.paho.org/handle/10665.2/51542.

Palència L, Espelt A, Rodríguez-Sanz M, Puigpinós R, Pons-Vigués M, Pasarín MI, et al. (2010). Socio-economic inequalities in breast and cervical cancer screening practices in Europe: influence of the type of screening program. *Int J Epidemiol*. 39(3):757–65. doi:10.1093/ije/dyq003 PMID:20176587

Partanen V-M, Anttila A, Heinävaara S, Pankakoski M, Sarkeala T, Bzhalava Z, et al. (2019). NordScreen – an interactive tool for presenting cervical cancer screening indicators in the Nordic countries. *Acta Oncol*. 58(9):1199–204. doi:10.1080/0284186X.2019.1615637 PMID:31106635

Paul P, Winkler JL, Bartolini RM, Penny ME, Huong TT, Nga T, et al. (2013). Screen-and-treat approach to cervical cancer prevention using visual inspection with acetic acid and cryotherapy: experiences, perceptions, and beliefs from demonstration projects in Peru, Uganda, and Vietnam. *Oncologist*. 18(12):1278–84. doi:10.1634/theoncologist.2013-0253 PMID:24217554

PHAC (2009). Performance monitoring for cervical cancer screening programs in Canada. Ottawa, Canada: Public Health Agency of Canada. Available from: https://www.canada.ca/en/public-health/services/chronic-diseases/cancer/performance-monitoring-cervical-cancer-screening-programs-canada.html.

Pham T, Bui L, Kim G, Hoang D, Tran T, Hoang M (2019). Cancers in Vietnam – burden and control efforts: a narrative scoping review. *Cancer Contr*. 26(1):1073274819863802. doi:10.1177/1073274819863802 PMID:31319695

Plotkin M, Besana GV, Yuma S, Kim YM, Kulindwa Y, Kabole F, et al. (2014). Integrating HIV testing into cervical cancer screening in Tanzania: an analysis of routine service delivery statistics. *BMC Womens Health*. 14(1):120. doi:10.1186/1472-6874-14-120 PMID:25271025

Ploysawang P, Rojanamatin J, Prapakorn S, Jamsri P, Pangmuang P, Seeda K, et al. (2021). National cervical cancer screening in Thailand. *Asian Pac J Cancer Prev*. 22(1):25–30. doi:10.31557/APJCP.2021.22.1.25 PMID:33507675

Poljak M, Seme K, Maver PJ, Kocjan BJ, Cuschieri KS, Rogovskaya SI, et al. (2013). Human papillomavirus prevalence and type-distribution, cervical cancer screening practices and current status of vaccination implementation in Central and Eastern Europe. *Vaccine*. 31(Suppl 7):H59–70. doi:10.1016/j.vaccine.2013.03.029 PMID:24332298

Ponti A, Anttila A, Ronco G, Senore C, Basu P, Segnan N, et al. (2017). Cancer screening in the European Union (2017). Report on the implementation of the Council Recommendation on cancer screening (second report). Brussels, Belgium: European Commission. Available from: https://ec.europa.eu/health/sites/default/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf.

Porter Novelli (2015). DocStyles 2015 methods. Washington (DC), USA: Porter Novelli. Available from: https://styles.porternovelli.com.

Public Health England (2017). Programme specific operating model for quality assurance of cervical screening programmes. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653740/CERVIX_PSOM.pdf.

Refaei M, Dehghan Nayeri N, Khakbazan Z, Yazdkhasti M, Shayan A (2018). Exploring effective contextual factors for regular cervical cancer screening in Iranian women: a qualitative study. *Asian Pac J Cancer Prev.* 19(2):533–9. doi:10.22034/APJCP.2018.19.2.533 PMID:29480997

Regionala Cancercentrum (2019). Cervical cancer prevention. Stockholm, Sweden. Available from: https://kunskapsbanken.cancercentrum.se/globalassets/vara-uppdrag/prevention-tidig-upptackt/gynekologisk-cellprovskontroll/vardprogram/nationellt-vardprogram-cervixcancerprevention.pdf.

République Algérienne Démocratique et Populaire (2014). Plan national cancer 2015–2019. Nouvelle vision stratégique centrée sur le malade. [in French] Available from: https://www.iccp-portal.org/sites/default/files/plans/Algerie_plan_national_cancer.compressed.pdf.

République de Madagascar, OMS (2016). Plan stratégique national de la lutte contre le cancer du col 2016–2020. [in French] Available from: https://www.iccp-portal.org/system/files/plans/PSNLCC.pdf.

RIVM (2020). Cervical cancer screening programme. Bilthoven, Netherlands: National Institute for Public Health and the Environment (RIVM). Available from https://www.rivm.nl/en/cervical-cancer-screening-programme.

Rogovskaya SI, Shabalova IP, Mikheeva IV, Minkina GN, Podzolkova NM, Shipulina OY, et al. (2013). Human papillomavirus prevalence and type-distribution, cervical cancer screening practices and current status of vaccination implementation in Russian Federation, the western countries of the former Soviet Union, Caucasus region and Central Asia. *Vaccine.* 31(Suppl 7):H46–58. doi:10.1016/j.vaccine.2013.06.043 PMID:24332297

Rojas Gómez B, Rodríguez Monegro N, Peguero R, Eusebio H, Mejía W, Fernández F (2010). Guías para el manejo de las neoplasias de cérvix. Primera edición. Santo Domingo, República Dominicana: Secretaría de Estado de Salud Pública y Asistencia Social. [in Spanish] Available from: https://extranet.who.int/ncdccs/Data/DOM_D1_Gu%C3%ADa%20Manejo%20%20de%20la%20Neoplasias.pdf.

Ronco G, Anttila A (2009). Cervical cancer screening in Europe – changes over the last 9 years. *Eur J Cancer.* 45(15):2629–31. doi:10.1016/j.ejca.2009.07.021 PMID:19695869

Sabik LM, Adunlin G (2017). The ACA and cancer screening and diagnosis. *Cancer J.* 23(3):151–62. doi:10.1097/PPO.0000000000000261 PMID:28537960

Sahasrabuddhe VV, Parham GP, Mwanahamuntu MH, Vermund SH (2012). Cervical cancer prevention in low- and middle-income countries: feasible, affordable, essential. *Cancer Prev Res (Phila).* 5(1):11–7. doi:10.1158/1940-6207.CAPR-11-0540 PMID:22158053

Sait KH (2009). Attitudes, knowledge, and practices in relation to cervical cancer and its screening among women in Saudi Arabia. *Saudi Med J.* 30(9):1208–12. PMID:19750269

Sancho-Garnier H, Khazraji YC, Cherif MH, Mahnane A, Hsairi M, El Shalakamy A, et al. (2013). Overview of cervical cancer screening practices in the extended Middle East and North Africa countries. *Vaccine.* 31(Suppl 6):G51–7. doi:10.1016/j.vaccine.2012.06.046 PMID:24331820

Sano H, Goto R, Hamashima C (2014). What is the most effective strategy for improving the cancer screening rate in Japan? *Asian Pac J Cancer Prev.* 15(6):2607–12. doi:10.7314/APJCP.2014.15.6.2607 PMID:24761871

Sauvaget C, Nishino Y, Konno R, Tase T, Morimoto T, Hisamichi S (2016). Challenges in breast and cervical cancer control in Japan. *Lancet Oncol.* 17(7):e305–12. doi:10.1016/S1470-2045(16)30121-8 PMID:27396648

Sawadogo B, Gitta SN, Rutebemberwa E, Sawadogo M, Meda N (2014). Knowledge and beliefs on cervical cancer and practices on cervical cancer screening among women aged 20 to 50 years in Ouagadougou, Burkina Faso, 2012: a cross-sectional study. *Pan Afr Med J.* 18:175. doi:10.11604/pamj.2014.18.175.3866 PMID:25419302

Secretaría de Salud de Honduras (2015). Protocol Sector Salud. PTO2: 2015. Protocolo para el tamizaje y tratamiento de lesiones premalignas para la prevención del cáncer cervicouterino. Tegucigalpa, Honduras: Gobierno de la República de Honduras, Secretaría de Salud. [in Spanish] Available from: https://extranet.who.int/ncdccs/Data/HND_D1_Protocolo%20C%C3%A1ncer%20C%C3%A9rvicouterino%20(30%20NOV).pdf

Secretaría de Salud de Mexico (2013). *Programa de acción específico: prevención y control del cáncer de la mujer 2013–2018. Programa Sectorial de Salud, Estados Unidos Mexicanos* [in Spanish]. Available from. https://www.gob.mx/cms/uploads/attachment/file/10046/PrevencionyControldelCancerdelaMujer_2013_2018.pdf.

Secretaría de Salud de México (2020). Centro Nacional de Excelencia Tecnológica en Salud (CENETEC). [in Spanish] Available from: https://www.gob.mx/salud/cenetec.

Secretaría de Salud, Instituto Nacional de Estadística & ICF International (2013). Encuesta Nacional de Demografía y Salud, ENDESA 2011–2012: informe resumen. Tegucigalpa, Honduras: Secretaría de Salud, Instituto Nacional de Estadística, ICF International. [in Spanish] Available from: https://www.ine.gob.hn/images/Productos%20ine/endesa/Informe%20Resumen%20ENDESA.pdf.

Selmouni F, Belakhel L, Sauvaget C, Abousselham L, Lucas E, Muwonge R, et al. (2019). Evaluation of the national cervical cancer screening program in Morocco: achievements and challenges. J Med Screen. 26(3):162–8. doi:10.1177/0969141318824627 PMID:30651034

Sengayi-Muchengeti M, Joko-Fru WY, Miranda-Filho A, Egue M, Akele-Akpo MT, N'da G, et al. (2020). Cervical cancer survival in sub-Saharan Africa by age, stage at diagnosis and Human Development Index: a population-based registry study. Int J Cancer. 147(11):3037–48. doi:10.1002/ijc.33120 PMID:32449157

Serbanescu F, Ruiz A, Suchdev DB (2010). Reproductive health survey Jamaica 2008: final report. Atlanta (GA), USA: Centers for Disease Control and Prevention. Kingston, Jamaica: National Family Planning Board. Available from: http://jnfpb.org/wp-content/uploads/2019/11/2008-RHS-Final-Report.pdf.

Sethom F, Besbes K, Cammoun M (1989). For an early diagnosis of cervical cancer by systematic vaginal smears – clinical and psychological approach. [in French] Tunis Med. 67(8–9):505–11. PMID:2799975

Sharkas G, Arqoub K, Khader Y, Nimri O, Shroukh W, Jadallah H, et al. (2017). Trends in the incidence of cervical cancer in Jordan, 2000-2013. J Oncol. 2017:6827384. doi:10.1155/2017/6827384 PMID:28932241

Shiferaw N, Salvador-Davila G, Kassahun K, Brooks MI, Weldegebreal T, Tilahun Y, et al. (2016). The single-visit approach as a cervical cancer prevention strategy among women with HIV in Ethiopia: successes and lessons learned. Glob Health Sci Pract. 4(1):87–98. doi:10.9745/GHSP-D-15-00325 PMID:27016546

Sigurdsson K (2010). Cervical cancer: cytological cervical screening in Iceland and implications of HPV vaccines. Cytopathology. 21(4):213–22. doi:10.1111/j.1365-2303.2010.00783.x PMID:20646020

Su S-Y, Huang J-Y, Ho C-C, Liaw Y-P (2013). Evidence for cervical cancer mortality with screening program in Taiwan, 1981–2010: age-period-cohort model. BMC Public Health. 13(1):13. doi:10.1186/1471-2458-13-13 PMID:23297757

Suhaimi AMAP, Rahman HA, Ong SK, Koh D (2020). Predictors of non-communicable diseases screening behaviours among adult population in Brunei Darussalam: a retrospective study. J Public Health. doi:10.1007/s10389-020-01240-z

Tangka FK, Howard DH, Royalty J, Dalzell LP, Miller J, O'Hara BJ, et al. (2015). Cervical cancer screening of underserved women in the United States: results from the National Breast and Cervical Cancer Early Detection Program, 1997–2012. Cancer Causes Control. 26(5):671–86. doi:10.1007/s10552-015-0524-5 PMID:25783455

Tran NT, Choe SI, Taylor R, Ko WS, Pyo HS, So HC (2011). Knowledge, attitude and practice (KAP) concerning cervical cancer and screening among rural and urban women in six provinces of the Democratic People's Republic of Korea. Asian Pac J Cancer Prev. 12(11):3029–33. PMID:22393985

Tranberg M, Andersen B (2018). HPV self-sampling for cervical cancer screening in Denmark. [in Danish] Ugeskr Laeger. 180(48):V07180475. PMID:30518468

Tranberg M, Bech BH, Blaakær J, Jensen JS, Svanholm H, Andersen B (2018). Preventing cervical cancer using HPV self-sampling: direct mailing of test-kits increases screening participation more than timely opt-in procedures – a randomized controlled trial. BMC Cancer. 18(1):273. doi:10.1186/s12885-018-4165-4 PMID:29523108

Tsu VD, Njama-Meya D, Lim J, Murray M, de Sanjose S (2018). Opportunities and challenges for introducing HPV testing for cervical cancer screening in sub-Saharan Africa. Prev Med. 114:205–8. doi:10.1016/j.ypmed.2018.07.012 PMID:30031013

UNICEF DPRK (2006). Analysis of the situation of children and women in the Democratic People's Republic of Korea. Pyongyang, Democratic People's Republic of Korea: United Nations Children's Fund. Available from: https://reliefweb.int/report/democratic-peoples-republic-korea/analysis-situation-children-and-women-democratic-peoples.

U.S. Department of Health and Human Services Health Resources and Services Administration (2019). Cervical cancer screening. Available from: https://www.hrsa.gov/sites/default/files/quality/toolbox/508pdfs/cervicalcancerscreening.pdf.

U.S. Legislative Counsel (2010). Compilation of Patient Protection and Affordable Care Act. 111th Congress, 2nd Session. Washington (DC), USA: U.S. House of Representatives. Available from: https://www.hhs.gov/sites/default/files/ppacacon.pdf.

US Preventive Services Task Force (2018). Screening for cervical cancer: US Preventive Services Task Force recommendation statement. JAMA. 320(7):674–86. doi:10.1001/jama.2018.10897 PMID:30140884

Vale DB, Anttila A, Ponti A, Senore C, Sankaranaryanan R, Ronco G, et al. (2019b). Invitation strategies and coverage in the population-based cancer screening programmes in the European Union. Eur J Cancer Prev.

28(2):131–40. doi:10.1097/CEJ.0000000000000426 PMID:29570103

Vale DB, Bragança JF, Zeferino LC (2019a). Cervical cancer screening in low- and middle-income countries. In: Farghaly S, editor. Uterine cervical cancer. Clinical and therapeutic perspectives. Cham, Switzerland: Springer; pp. 53–9. doi:10.1007/978-3-030-02701-8_4

van der Veen N (2017). Framework for the execution of cervical cancer population screening. Bilthoven, Netherlands: National Institute for Public Health and the Environment.

Vastbinder MB, Castillo C, Bekkers RL (2010). Barriers to follow-up of abnormal Papanicolaou smears among women in Leon, Nicaragua. Trop Doct. 40(1):22–6. doi:10.1258/td.2009.090076 PMID:20008060

von Karsa L, Anttila A, Ronco G, Ponti A, Malila N, Arbyn M, et al. (2008). Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening. First report. Brussels, Belgium: European Commission. Available from: https://ec.europa.eu/jrc/sites/default/files/cancer_screening.pdf.

von Karsa L, Arbyn M, De Vuyst H, Dillner J, Dillner L, Franceschi S, et al. (2015). European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Papillomavirus Res. 1:22–31. doi:10.1016/j.pvr.2015.06.006

Wahidin M (2018). Overview of ten years (2007–2016) cervical and breast cancer screening program in Indonesia. J Global Oncol. 4(Suppl 2):51s. doi:10.1200/jgo.18.21100

Wang SM, Qiao YL (2015). Implementation of cervical cancer screening and prevention in China – challenges and reality. Jpn J Clin Oncol. 45(1):7–11. doi:10.1093/jjco/hyu188 PMID:25398583

WHO (2007). Everybody's business. Strengthening health systems to improve health outcomes. WHO's framework for action. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/healthsystems/strategy/everybodys_business.pdf?ua=1.

WHO (2013). Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/.

WHO (2014a). Saving women's lives in Mongolia through cancer screening. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/features/2014/cancer-mongolia/en/.

WHO (2014b). Comprehensive cervical cancer control: a guide to essential practice. 2nd edition. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/144785.

WHO (2015). The Kingdom of Cambodia health system review. Health systems in transition, vol. 5, no. 2. Manila, Philippines: World Health Organization Regional Office for the Western Pacific. Available from: https://apps.who.int/iris/handle/10665/208213.

WHO (2017). The Republic of Indonesia health system review. Health systems in transition, vol. 17, no. 1. New Delhi, India: World Health Organization Regional Office for South East Asia. Available from: https://apps.who.int/iris/handle/10665/254716.

WHO (2018). Improving data for decision-making: a toolkit for cervical cancer prevention and control programmes. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/279420.

WHO (2020a). Noncommunicable diseases and their risk factors. STEPS Country Reports. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/ncds/surveillance/steps/reports/en/.

WHO (2020b). Cancer country profile, Syrian Arab Republic. Geneva, Switzerland: World Health Organization. Available from: https://www.iccp-portal.org/system/files/plans/SYR_2020.pdf.

WHO (2020c). Cancer country profiles 2020. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/cancer/country-profiles/en/.

WHO (2020d). Costing the National Programme for Secondary Prevention of Cervical Cancer: Myanmar, 2020–2024. Geneva, Switzerland: World Health Organization. Available from: https://cdn.who.int/media/docs/default-source/cervical-cancer/myanmar-cxca-costing-report-20201109-2.pdf?sfvrsn=6cbe8fdb_6.

WHO (2020e). Cancer country profile, Burkina Faso. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/cancer/country-profiles/BFA_2020.pdf?ua=1.

WHO (2020f). Cancer country profile, Ethiopia. Geneva, Switzerland: World Health Organization. Available from: https://www.iccp-portal.org/system/files/plans/ETH_2020.pdf.

WHO (2020g). Cancer country profile, South Africa. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/cancer/country-profiles/ZAF_2020.pdf?ua=1.

WHO (2020h). Cancer country profile, Somalia. Geneva, Switzerland: World Health Organization. Available from: https://www.iccp-portal.org/system/files/plans/SOM_2020.pdf.

WHO (2020i). Cancer country profile, Tunisia. Geneva, Switzerland: World Health Organization. Available

from: https://www.iccp-portal.org/system/files/plans/TUN_2020.pdf.

WHO/PAHO (2013). Monitoring national cervical cancer prevention and control programmes: quality control and quality assurance for visual inspection with acetic acid (VIA)-based programmes. Geneva, Switzerland: World Health Organization, Pan American Health Organization. Available from: https://apps.who.int/iris/handle/10665/79316.

WHO/SEARO (2015). Strategic framework for the comprehensive control of cancer cervix in South-East Asia Region. New Delhi, India: World Health Organization Regional Office for South-East Asia. Available from: https://apps.who.int/iris/handle/10665/152098.

Wiesner C, Cendales R, Murillo R, Piñeros M, Tovar S (2010). Following-up females having an abnormal Pap smear in Colombia. [in Spanish] *Rev Salud Publica (Bogota)*. 12(1):1–13. doi:10.1590/S0124-00642010000100001 PMID:20628695

Yabroff KR, Saraiya M, Meissner HI, Haggstrom DA, Wideroff L, Yuan G, et al. (2009). Specialty differences in primary care physician reports of Papanicolaou test screening practices: a national survey, 2006 to 2007. *Ann Intern Med*. 151(9):602–11. doi:10.7326/0003-4819-151-9-200911030-00005 PMID:19884621

Zhang M, Zhong Y, Zhao Z, Huang Z, Zhang X, Li C, et al. (2018). Cervical cancer screening rates among Chinese women – China, 2015. *China CDC Weekly*. 2(26):481–86. doi:10.46234/ccdcw2020.128

Zhao J, Mao Z, Fedewa SA, Nogueira L, Yabroff KR, Jemal A, et al. (2020). The Affordable Care Act and access to care across the cancer control continuum: a review at 10 years. *CA Cancer J Clin*. 70(3):165–81. doi:10.3322/caac.21604 PMID:32202312

3. PARTICIPATION IN SCREENING FOR CERVICAL CANCER

3.1 Negative and positive determinants of participation

Achieving high participation is an important element of any screening programme. There are many reasons why women do not use preventive services (Table 3.1). To capture this multidimensional causal pathway, the Social Determinants of Health Framework (Solar & Irwin, 2010; Fig. 3.1) considers health outcomes to be the result of interactions between contextual and policy factors, structural factors related to women's socioeconomic conditions, and intermediate factors, which include determinants at the individual level and at the health system level (programme and provider levels). When analysing variables that are negatively or positively related to screening participation in a specific setting, it is important to understand the levels at which factors are operating and how they are interconnected.

3.1.1 Health policy determinants

Contextual aspects, including education, employment, and social protection policies, act as modifiers or buffers that influence the effects of socioeconomic status on health outcomes and well-being in social groups (Solar & Irwin, 2010). An analysis of data from 15 low-income countries that participated in the 2003 World

Health Survey (Akinyemiju, 2012) found that a country's health expenditure (as a percentage of gross domestic product) was a significant determinant of participation in cervical cancer and breast cancer screening. This finding suggests that irrespective of individual and neighbourhood factors, investment in health infrastructure has the potential to significantly improve cancer screening rates within a country, for example through better equipment and trained personnel in hospitals.

In their analysis of the effect on cancer care outcomes of disruptions in health insurance coverage in the USA, Yabroff et al. (2020) highlighted how changes in broader policies can exacerbate disruptions in insurance coverage and can increase disparities. For example, the emergence of work requirements for some state Medicaid programmes may increase the prevalence of coverage disruptions. Also, broader employment trends, such as the increased prevalence of gig workers (independent contractors) and associated income fluctuations, may increase disruptions in coverage in a population that faces frequent changes in eligibility for subsidies and coverage affordability. In Mexico, the health-care reform implemented in 2003 to provide universal health coverage resulted in a substantial increase in cervical cancer screening coverage, from 30.0% in 2000 to 48.5% in 2012 (Goss et al., 2013). Competing health priorities

Table 3.1 Positive and negative determinants of screening participation

Positive determinants	Negative determinants
Health policy determinants	
Higher national health expenditure	Lack of universal health coverage
Investments in health infrastructure	Fee-paid services
Universal health coverage	
Structural determinants	
Higher socioeconomic status; gender equity (participation in household decisions)	Low socioeconomic status; gender inequality (low control over household decisions; gender violence)
Higher levels of education	Low education level
Being employed	Unemployment
Younger age	Older age
Being married	Single relationship status
Longer time spent in destination country (for immigrants)	Immigrant status; member of disadvantaged racial or ethnic group
Health insurance	Lack of health insurance
Urban residence	Rural residence
	Being transgender, non-binary, or lesbian
Intermediate determinants at the individual level	
Health literacy; cervical cancer knowledge; awareness of perceived benefits of screening	Lack of knowledge about cervical cancer; low self-assessed risk of cervical cancer
Previous use of health-care or preventive services; engagement with health-care services; history of ever having had a gynaecological examination	Lack of recent contact with health-care services; long time elapsed since last screening or no history of cervical cancer screening
History of using contraception	No use of contraception
Being unconcerned with regard to the sex of the health-care provider	Rejection of gynaecological examination by male health-care providers
Able to talk with family and/or friends about cervical screening; family support; childcare options	Lack of social support; lack of childcare
	Having experienced sexual assault
	Female genital mutilation
	Being incarcerated
	Having a disability
	Discomfort or previous negative experience with gynaecological examination; negative attitude towards cervical cancer screening
	Feelings of shame or embarrassment
	Fear of cancer
Intermediate determinants at the health system level	
Organized screening programmes	Opportunistic screening
Adequate availability and distribution of primary health-care and gynaecology services	Low availability of primary health-care or gynaecology centres
High adherence by health-care providers to programmatic guidelines and recommendations	Low adherence by health-care providers to programmatic guidelines and recommendations
Good-quality services, with adequate infrastructure, supply provision, and trained health-care workforce	Lack of supplies and screening or treatment infrastructure; lack of trained health-care workforce
Use of HPV self-sampling as screening strategy	Screening only through gynaecological examination
Screening, diagnosis, and/or treatment included as part of a health insurance package	Fee-paid services
Use of screening information systems	Lack of screening information systems

Table 3.1 (continued)

Positive determinants	Negative determinants
Intermediate determinants at the health provider level	
Encouragement from health-care providers to get screened	Lack of encouragement from health-care providers
Use of communication strategies and tools between health-care providers and women; navigation services	Screening services that do not meet women's needs (appointment days and hours, etc.); lack of communication or navigation strategies
Option to choose male or female health-care provider	Male health-care provider only
Women and health-care providers having the same social and cultural background; screening offered by community health workers	Lack of community health workers or promoters

HPV, human papillomavirus.
Table compiled by the Working Group.

and a lack of emphasis on preventive health have also been shown to be barriers to the implementation of effective population-based cervical cancer screening programmes in low- and middle-income countries (LMICs) (Mandal & Basu, 2018).

3.1.2 Structural determinants

The main structural determinant of screening participation in women is social inequality (Table 3.1). Women with low socio-economic status and education level, without health insurance, and with reduced access to health care tend to have lower rates of screening (IARC, 2005). These main determinants were also identified by reviews of studies in LMICs (Williams-Brennan et al., 2012) and specific to Latin America (Nuche-Berenguer & Sakellariou, 2019). Most of this evidence was produced in contexts in which cytology-based screening is the standard of care, but evidence from studies in which screening was carried out with human papillomavirus (HPV)-based testing or visual inspection with acetic acid (VIA)-based testing showed a similar impact of these structural socioeconomic inequalities (Harder et al., 2018b; Brandão et al., 2019).

An analysis of data from World Health Surveys from 57 countries showed that only 31% of women in the poorest global wealth decile have ever had a pelvic examination, compared with 91% of women in the richest global wealth decile. Effective cervical cancer screening (the proportion of eligible women who report that they have had a pelvic examination and Pap test in the previous 3 years) was 9% in the poorest decile and 64% in the richest decile (Gakidou et al., 2008). Being younger (Barbadoro et al., 2015; Giorgi Rossi et al., 2015; Broberg et al., 2018; Buehler et al., 2019) and living in an urban area (Akinyemiju, 2012) have been reported to be important positive determinants of participation. Belonging to an ethnic minority group (an indicator of social inequity) (Soneji & Fukui, 2013) and being a migrant (Harder et al., 2018a, b; Adunlin et al., 2019; Bacal et al., 2019) have been reported to be negative determinants of participation.

There is much less empirical evidence about how gender inequality, such as the differential access of women to structural resources, power, authority, and control (WHO, 2007), affects access to screening services. An analysis of knowledge about cervical cancer and screening using the 2014 Kenya Demographic and Health Survey reported that women who face gender inequality (i.e. have no control over decision-making about their own health care and/or household money) and gendered norms on intimate partner violence were less likely to be knowledgeable about cervical cancer screening and to

Fig. 3.1 Social Determinants of Health Framework
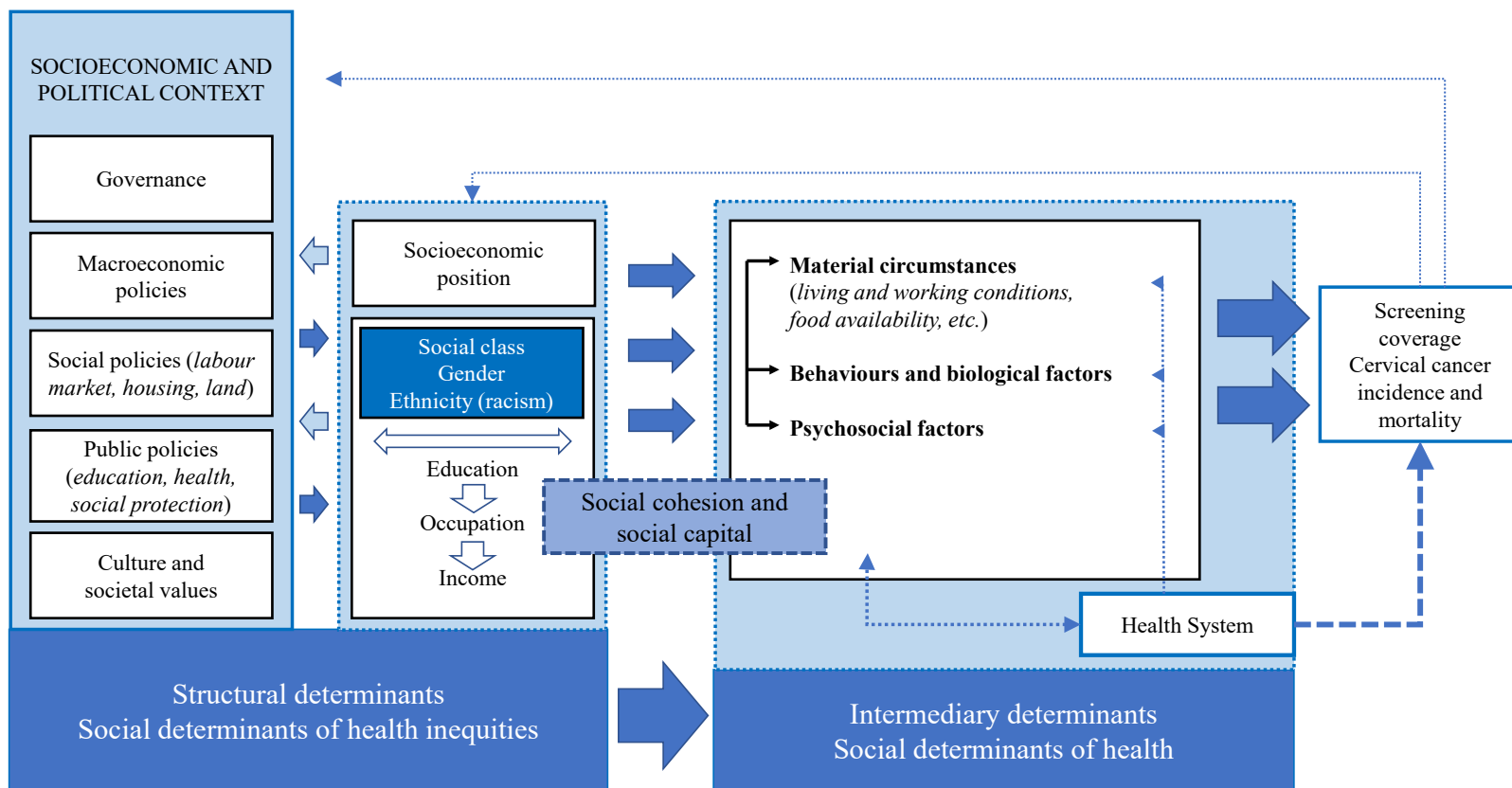
undergo screening compared with women who did not face these challenges ([Kangmennaang et al., 2018](#)).

Sexual orientation is also a main determinant of participation; transgender men, lesbians, and non-binary people are less likely to be screened ([Connolly et al., 2020](#)). Potential barriers to routine cervical cancer screening for lesbians include the perception that they have a lower risk of cervical cancer, discrimination and homophobia in the health-care system, and a lack of awareness in health-care providers about the disease risk in this population ([Tracy et al., 2013](#)). Barriers to screening in transgender men ([Weyers et al., 2021](#)) include female-only waiting rooms, woman-centred and heteronormative patient education materials, the use of language that is not gender-neutral by health-care providers during the screening examination, and stigma and discrimination by health-care providers and insurance providers, which can lead to postponement of care.

3.1.3 Intermediate determinants at the individual level

Having had previous contacts with the health-care system is an important determinant of screening participation ([IARC, 2005](#); [Williams-Brennan et al., 2012](#)) through several mechanisms, one of which is increased health literacy. Knowledge and awareness about cervical cancer and the role of screening in disease prevention, as well as knowing another person who has already been screened, are positive determinants of participation ([IARC, 2005](#); [Nwobodo & Ba-Break, 2015](#); [Visanuyothin et al., 2015](#); [Idowu et al., 2016](#); [Bou-Orm et al., 2018](#)). Awareness of risk has also been shown to have an impact on a woman's decision to be screened ([Dhendup & Tshering, 2014](#); [Morema et al., 2014](#)).

"Lack of time" is a negative determinant of participation ([Szarewski et al., 2011](#); [Arrossi et al., 2016](#); [Restivo et al., 2018](#)). Gender inequality may mean that women have to deal with work demands while having major responsibilities for domestic activities and childcare. In addition, socially disadvantaged women tend to have precarious jobs, without social protection or the flexibility to attend health services. In a study that analysed women's preference for HPV self-sampling in Argentina, the main reasons for choosing self-sampling at home were related to time saved; this method of screening does not interfere with a woman's family and domestic responsibilities, which prevent them from attending a health centre, and avoids barriers to accessing health services, such as a shortage of appointments and physician absenteeism ([Arrossi et al., 2016](#)). Furthermore, in low-income settings, where many women live in areas with poor public transportation and road infrastructure, the "lack of time" variable may reflect not only a woman's difficulty in finding the time to go to the health centre, but also greater difficulty accessing health services because of the barriers associated with the transportation infrastructure and non-responsive health services ([Osingada et al., 2015](#)).

Feelings of shame or embarrassment ([Szarewski et al., 2011](#); [Darlin et al., 2013](#); [Restivo et al., 2018](#)) have been reported to be barriers to screening in many different world regions and settings ([Chorley et al., 2017](#); [Lim & Ojo, 2017](#); [Liebermann, et al., 2018](#); [Marlow et al., 2019](#)), mainly linked to the gynaecological examination and stigma associated with being diagnosed with a reproductive health problem or with a disease that is perceived as being caused by poor hygiene or promiscuous behaviour. A systematic review summarized reported barriers that prevented women from using cervical cancer screening services in sub-Saharan Africa ([Lim & Ojo, 2017](#)); it found that women experienced stigmatization and embarrassment when accessing cervical screening services. The authors reported that because clinician-collected screening involves pelvic examination and may be combined with screening and treatment of a

reproductive or sexually transmitted infection, it can have a negative connotation for a woman. In a systematic review of qualitative literature about women's perceptions and experiences of cervical screening and a thematic analysis of barriers to cervical screening participation in organized programmes, some women perceived cervical cancer screening as a social threat, because a positive test result would cause anxiety and fear of stigma and could result in them being labelled as promiscuous (Chorley et al., 2017). Previous experiences of sexual assault or female genital mutilation have also been found to be barriers to participation (Marques et al., 2020).

Fear of cancer and anxiety are other key barriers to screening (IARC, 2005; Szarewski et al., 2011; Williams-Brennan et al., 2012; Arrossi et al., 2016; Restivo et al., 2018). Liebermann et al. (2018) pointed out that fear has several layers, including fear or perceived pain of the Pap procedure, fear of the results of the Pap test, and fear of cancer, which is seen as an incurable disease. Similarly, Chorley et al. (2017) found that fear and anxiety were linked to fear of cancer through anticipation of pain, suffering, and death, and to concerns in younger women about the impact on fertility. A study to measure the psychosocial impact of HPV testing in 163 HPV-positive women in Argentina reported that worries about cancer and associated treatment had the greatest negative psychosocial impact (Arrossi et al., 2020). Several studies in Latin America reported similar findings (Smith et al., 2014; León-Maldonado et al., 2016). The quality of care and the information provided or omitted by physicians have also been shown to contribute to fear and anxiety (Schoenberg et al., 2010).

Encouragement and social support from a woman's family, friends, or spouse have been found to be positive determinants of participation (Williams-Brennan et al., 2012). Being in a partnership also increases the probability of being screened (Williams-Brennan et al., 2012;

Visanuyothin et al., 2015; Hanske et al., 2016; Bou-Orm et al., 2018; Harder et al., 2018a).

Little information is available about screening rates in women in prison; studies have shown both increased and decreased participation in this group of women (Brousseau et al., 2019). A study that analysed female prisoners' perceptions of screening (Magee et al., 2005) reported that uncomfortable examination was the main issue; this related to the use of inappropriately sized speculums and the rough manner of health-care providers. The prison infrastructure was also cited as problematic, because of a lack of privacy, poorly maintained facilities, no standard process for scheduling, long delays, inconsistency for costs to the inmate, and the lack of a method to report results.

Women with a disability underuse preventive cervical cancer screening services compared with the general population (Ramjan et al., 2016). These women not only have lower levels of health insurance, which affects their access to screening, but they also face health-care provider barriers, including physicians' attitudes, poor knowledge, misconceptions, and lack of understanding of the disability. Physical barriers are also an important problem for women with a disability, especially those related to access to health-care facilities and inadequate equipment, such as examination tables for Pap tests.

3.1.4 Intermediate determinants at the programme or service organization level

Health system characteristics and the way screening programmes are organized are intermediate variables that can moderate the impact of social and gender inequalities; they are therefore major determinants of coverage. A systematic review describing the implementation of decentralized cervical cancer prevention services in rural Africa reported that health workforce shortages and lack of outreach were among the

most common supply-side barriers to cervical screening (Rahman et al., 2019). The availability and distribution of primary health-care and gynaecology services according to urban or rural settings and population density are also determinants of screening participation. A study of 3380 women in France, where universal health care is provided, showed that after individual characteristics were taken into account, women in settings with poor access to a gynaecologist had lower rates of screening participation (Araujo et al., 2017).

Another important set of considerations are the funding mechanisms for cervical cancer screening and treatment. Whether screening is included as part of a health insurance package or has to be paid for out-of-pocket is a significant determinant of screening participation. Lack of health insurance is an indicator of how health services are funded (WHO, 2008), and women who are not insured or who have disruptions in health insurance coverage are less likely to participate in screening (Williams-Brennan et al., 2012; Yabroff et al., 2020). An analysis in Argentina found that providing the HPV test free of charge to women with no health insurance was a key factor for improved screening participation (Arrossi et al., 2017).

How screening programmes are set up (organized vs opportunistic screening) is another important consideration. An organized screening programme implies that there is an active strategy to reach out to all women defined as eligible in a population at a defined frequency, and that a prioritized programme is in place with adequate funding, a system to ensure follow-up and treatment, an information and monitoring system and quality assurance procedures, and mechanisms to ensure compliance with norms and regulations by health-care providers and institutions. In general, opportunistic screening tends to increase health and social inequalities, whereas organized programmes with active invitation procedures tend to increase access for socially disadvantaged women (Palència et al., 2010). The use of screening information systems also facilitates screening participation at the health system level (Arrossi et al., 2015a).

3.1.5 Intermediate determinants at the health provider level

Good-quality service delivery and good patient–provider relationships and communication are important facilitators of screening. Studies have shown that women are more likely to participate in screening if they have a good relationship with their health-care provider, they feel they are treated well, and they receive adequate information and responses to their questions (IARC, 2005; Darlin et al., 2013; Restivo et al., 2018). The use of counselling strategies to provide women with information about the screening and treatment process is also a facilitator of screening (León-Maldonado et al., 2014). In contrast, previous negative experiences with gynaecological examinations and health service delivery are barriers to screening (Szarewski et al., 2011; Darlin et al., 2013).

Factors related to the way in which health-care services are organized have also been found to affect screening participation. Systems for booking appointments, appointment hours and days, and waiting times can be barriers or facilitators, depending on whether health-care delivery is organized to respond to the needs of women (Nwobodo & Ba-Break, 2015; Visanuyothin et al., 2015; Restivo et al., 2018; Ryan et al., 2019). In a qualitative study of 3049 women in Jujuy, Argentina, the main reasons for choosing HPV self-sampling for cervical cancer screening were related to health-care organization challenges, such as a shortage of appointments and physician absenteeism (Arrossi et al., 2016). Other determinants of screening include the high turnover of trained professionals (Rahman et al., 2019), adherence by health-care providers to programme guidelines

and recommendations ([Arrossi et al., 2010](#)), and the socioeconomic level of the area in which the health-care provider office is situated ([Serman et al., 2020](#)). A significant negative determinant of screening participation at the health-care provider level in low-resource settings is the lack of supplies or infrastructure needed for screening or treatment ([Rahman et al., 2019](#)). This includes the lack of anaesthesia to provide treatment, the lack of reliable electricity, and difficulties in travelling to rural locations.

Screening performed by male health-care providers is a major barrier to screening participation in a variety of settings and countries ([IARC, 2005](#); [Dhendup & Tshering, 2014](#)); in contrast, screening provided by health-care workers of the same social and cultural background as their patients acts as a positive determinant ([Arrossi et al., 2015a](#); [Thompson et al., 2017](#); [Kobetz et al., 2018](#)).

The screening technology used is an important component of the health system dimension; whether cytology-based screening, HPV testing, or VIA is used will affect women's participation in preventive and treatment services. The effect of the use of HPV self-sampling kits on screening participation rates is discussed in Section 3.2.2.

3.1.6 Informed decision-making

An informed choice is one that is based on relevant knowledge, that is consistent with the decision-maker's values, and that is implemented behaviourally ([Marlow & Waller, 2014](#)). Informed choices give patients the opportunity to receive their preferred health-care options by choosing from among specified alternatives ([McCaffery et al., 2011](#)). In 2006, the International Patient Decision Aid Standards Collaboration established a checklist of quality criteria for decision aids, which includes categories focusing on essential content (providing balanced information, presenting probabilities, clarifying values, and guiding deliberation and communication),

development (systematic methods, balanced presentation, up-to-date and transparent evidence, and plain language), and evaluation (informed and values-based decisions) ([Elwyn et al., 2006](#)). Two studies in Australia showed that when women were offered evidence-based information, they selected a course of management appropriate to their practical, health, or psychological circumstances ([McCaffery et al., 2008](#), [2011](#)).

However, in spite of the importance of providing women with information so they can make an informed choice about whether to be screened, little evidence exists about how this affects participation in screening, especially in LMICs. A study in Norway evaluated whether women's stated intention to participate in screening and pursue treatment changed when additional information on screening-related harms was provided; it was found that additional information did not significantly alter women's stated intentions to screen ([Iyer et al., 2019](#)). A study in Australia found that a large proportion of women preferred to be involved in decision-making for both routine Pap tests (87%) and follow-up for abnormal results (89%). Most women wanted information on screening benefits (77%) and risks (70%); of these, 85% wanted this information before screening ([Dieng et al., 2013](#)). [Kim et al. (2017)](#) analysed how Korean immigrant women living in the USA made decisions about Pap tests according to three prototypes of shared decision-making in medical encounters: (i) a hierarchical model, in which the decision is made by health-care providers; (ii) an informed model, in which the decision is made by patients after reviewing alternative options; and (iii) a shared decision-making model, in which the decision is made collaboratively by health-care providers and patients on the basis of shared information. They found that for most women in the study, their preferred roles in decision-making were autonomous, but that for some they were hierarchical, collaborative (with the

physician for some participants and with their spouse for others), and peer-influenced. Barriers to informed decision-making are low education level, lack of knowledge, and differences between women and health-care providers in culture, social values, and language (Suurmond & Seeleman, 2006).

3.2 Interventions to increase screening participation

Cytology-based screening has been the standard of care for more than 70 years (see Section 4.3.1), but achieving high coverage is a challenge, especially in women of low socioeconomic status and/or in low-resource settings. One issue is that Pap tests are done through a gynaecological examination by health-care providers. This is also the case for VIA, which is proposed for settings where the development of cytology-based screening programmes is hampered by a lack of resources (WHO, 2013). The development of HPV testing has changed the scenario, because self-collection of samples for HPV testing has the potential to reduce barriers to access and increase screening participation. This section provides separate analyses of strategies to increase participation of women in cytology-based screening (Pap tests with clinician-collected samples) (Table 3.2) and strategies to increase participation of women in screening using HPV self-sampling (Table 3.3).

3.2.1 Interventions to increase participation in cytology-based screening

The 2005 *IARC Handbook* (IARC, 2005) reported that invitation strategies based on telephone invitations, person-to-person approaches, community campaigns, and educational interventions were effective in increasing participation in screening, depending on the context and settings. A review of studies published since 2005 is presented in the following sections.

(a) Invitation strategies

Based on a systematic review (Musa et al., 2017), measures such as invitation letters (with or without a follow-up telephone contact), making appointments, and sending reminders to patients who are due or overdue for screening all have a significant effect on improving participation and cervical cancer screening rates in populations at risk. An earlier meta-analysis of 12 randomized controlled trials (RCTs) of interventions to increase participation or informed participation in cervical cancer screening, which included 99 651 participants, found that screening participation in women who received invitation letters to attend cervical screening was significantly higher than that in women who received usual care or no invitation (relative risk [RR], 1.44; 95% confidence interval [CI], 1.24–1.52) (Everett et al., 2011).

The evidence from selected cytology-based RCTs using invitation strategies carried out in the general population since 2005 is presented in Table 3.2. Studies were conducted in Europe ($n = 5$), Asia ($n = 2$), Australia ($n = 2$), Africa ($n = 1$), and the USA ($n = 1$). Study participants were mainly adult women, most often non-respondents in organized screening programmes (studies in Australia, Denmark, and Sweden) or women from population groups with low screening participation in settings where screening is opportunistic.

The formats of the invitations are very varied. Invitations may be extended through telephone calls (Dietrich et al., 2006), mailed letters with or without leaflets or telephone call reminders (Morrell et al., 2005; Chumworathayi et al., 2007; de Jonge et al., 2008; Jensen et al., 2009; Mullins, 2009; Rashid et al., 2013; Radde et al., 2016; Acera et al., 2017), emails (Adonis et al., 2017), or text messages (Rashid et al., 2013; Firmino-Machado et al., 2018). Even with the same strategy (e.g. an invitation by letter), it is not possible to control for all the variables that may have an influence on

Table 3.2 Studies on strategies to increase participation of women in cytology-based screening

Reference Country or territory	Study type Intervention	Control group	Key outcomes
Invitation strategies			
Morrell et al. (2005) Australia	RCT Reminder letter to have a Pap test	No letter	Pap test rates in the intervention group were significantly higher than those in the control group (HR, 1.54; 95% CI, 1.43–1.67)
Dietrich et al. (2006) USA	RCT Telephone calls from prevention care managers to address screening barriers and assist with booking appointments, communicating with clinicians, and ensuring women had transportation to their appointments	Preventive health education guide + one telephone call to answer their questions and direct them to their primary care clinician for preventive care	7% (95% CI, 3–11%) increase from baseline for the intervention group. No significant change in the control group
Chumworathayi et al. (2007) Thailand	Quasi-RCT Appointment invitation letter offering dates for Pap testing in the near future	Baseline interviews in their homes + health education	At follow-up, 44.7% of women in the intervention group and 25.9% of women in the control group had been screened (*P* = 0.001)
de Jonge et al. (2008) Belgium	Quasi-RCT Invitation letter for cervical cancer screening	No invitation letter	6.4% (95% CI, 5.9–6.9%) increase in the proportion of women reporting for Pap testing, compared with the control group
Jensen et al. (2009) Denmark	Cluster RCT Normal invitation plus targeted letter signed by their GP plus GP intervention: GPs were visited by a facilitator who identified avenues for quality improvement related to cervical cancer screening and offered help with sending screening reminders to patients	Usual care. Women received a normal invitation letter that is sent to all women every 3 yr	Overall, women in the intervention group were 1.17 (95% CI, 1.04–1.30) times as likely to report for Pap testing during the study period as those in the control group
Mullins (2009) Australia	RCT Group 1: A targeted reminder letter, focusing on the heightened risks of cervical cancer later in life and the importance of continuing Pap test screening until age 70 yr Group 2: A general reminder letter, including general information about the importance of Pap test screening, but with no mention of specifics related to Pap test screening later in life	No letter	After 11 wk, 4.3% (95% CI, 3.7–4.9%) of women in the targeted letter group, 4.7% (95% CI, 4.1–5.3%) of women in the general letter group, and 1.6% (95% CI, 1.2–1.9%) of women in the control group had reported for Pap testing

Table 3.2 (continued)

Reference Country or territory	Study type Intervention	Control group	Key outcomes
Rashid et al. (2013) Malaysia	RCT 4-arm intervention: Group 1: Invitation letter Group 2: Registered letter Group 3: Text message Group 4: Telephone call In all 4 groups, women received the same information: that they would have to attend for a repeat Pap test within 1 mo from the date the letter was received	Not available	The participation rates of Pap testing in women who received recall by letter, registered letter, text message, and telephone call were 23.86%, 23.04%, 32.93%, and 50.89%, respectively Compared with women who received the standard letter, those who received the invitation through a telephone call were more likely to attend for a repeat Pap test (OR, 2.38; 95% CI, 1.56–3.62)
Radde et al. (2016) Germany	Randomized population-based cohort study Group A: Invitation letter Group B: Invitation letter and information brochure	No invitation	The cervical cancer screening participation rate was 91.8% in the intervention groups, compared with 85.3% in the control group ($P < 0.001$), with a 6.6% increase in participation and an adjusted OR of 2.69 (95% CI, 2.15–3.37). There was no significant difference between intervention groups A and B
Acera et al. (2017) Spain	Community-based RCT Group 1: Personalized invitation letter Group 2: Personalized invitation letter and informative leaflet Group 3: Personalized invitation letter + informative leaflet + personalized telephone call	Spontaneous request for cervical cancer screening	Screening participation attributed to the intervention was 18.6%, 17.4%, and 23.0% in groups 1, 2, and 3, respectively. The total increase in participation was 20% in the 3 intervention groups combined and 9.1% in the control group ($P < 0.001$) Participation was significantly higher in intervention group 3 (84.4%) than in the other intervention groups ($P < 0.001$)

Table 3.2 (continued)

Reference Country or territory	Study type Intervention	Control group	Key outcomes
Adonis et al. (2017) South Africa	Prospective longitudinal RCT Group 1 (loss-framed): Email messages highlighting the risk of cervical cancer and the danger associated with not participating in Pap test screening Group 2 (gain-framed): Email messages highlighting the health-promoting role of routine Pap test screening and that this is a way to ensure good long-term health outcomes Group 3 (neutral message): Email message outlining Pap test screening recommendation In the 3 groups, messages were accompanied by encouragement to contact their medical practitioner to discuss Pap test screening	Not available	No statistically significant differences were found in the Pap test screening participation rates between the 3 groups
Firmino-Machado et al. (2018) Portugal	RCT Two-arm intervention: Invitation through automated or customized text messages and telephone calls, followed by text message reminders of the appointments Participants were randomly assigned to two models of invitation, used both in text messages and in automated telephone calls: (i) neutral – formal writing to inform women that a screening appointment was scheduled (standard communication style in primary care); (ii) positive – motivational communication style	Letter of invitation	39.0% of women in the intervention group were screened vs 25.7% in the control group ($P < 0.001$)
Educational interventions			
Mock et al. (2007) USA	RCT Lay health worker outreach plus media education campaign consisting of Vietnamese-language television, radio, and newspaper advertisement announcements about cervical cancer and Pap test screening. In addition, booklets, reminder cards, posters, and calendars with messaging about Pap test screening were distributed at strategic points in the community	Media education campaign	At baseline, 65.8% of women in the intervention group reported having had at least one Pap test. After the study period, this increased to 81.8%, an increase of 16.0% ($P < 0.001$). In the control group, the percentage of women ever screened increased by 5.4% ($P < 0.001$)

Table 3.2   (continued)

Reference Country or territory	Study type Intervention	Control group	Key outcomes
Hiatt et al. (2008) USA	Quasi-experimental controlled trial Outreach strategy to educate participants in small groups and one-on-one settings using lay health workers	Inreach strategies included updates for providers on screening guidelines, the use of patient models to improve skills in breast and pelvic examination, and the institution of computer reminders	Reports of Pap test in the previous 3 yr did not differ significantly in pre-test and post-test surveys
Mishra et al. (2009) American Samoa	RCT An educational programme comprising a cervical cancer education booklet, skill-building and behavioural exercises, and group discussion sessions. The content was culturally tailored and focused on the community's role in addressing cervical cancer. Women received a US$ 5 payment for each educational session they attended	Opportunistic screening	Women in the intervention group were found to be twice as likely to report for screening (OR, 2.0; 95% CI, 1.3–3.2)
Taylor et al. (2010) USA	RCT Lay health workers (who were bilingual Vietnamese women) attempted to visit the homes of participants to share with them a culturally tailored educational DVD and pamphlet that had information about cervical cancer and screening. They also used visual aids in the home visit to highlight the importance of screening. Lay health workers also provided follow-up calls 1 mo after their visit. If women could not be contacted at home or did not permit home visits, they were sent the DVD and pamphlet	Participants received mailed educational material about physical activity and a pedometer	Ever-screened women in the intervention group were significantly more likely to report Pap testing ($P < 0.2$) than were ever-screened women in the control group (31% vs 13%; OR, 3.15; 95% CI, 1.20–8.27) There were no significant differences between the groups for women who had never been screened
O'Brien et al. (2010) USA	RCT Cervical cancer educational intervention led by community health workers (*promotoras*). Women participated in two 3-h group sessions led by *promotoras* that focused on cervical cancer and screening. Participants were also given relevant reading materials	Usual care (unspecified)	The Pap test participation rate was higher in the intervention group than in the control group (71% vs 22%; $P = 0.004$)

Table 3.2 (continued)

Reference Country or territory	Study type Intervention	Control group	Key outcomes
Nuño et al. (2011) USA	RCT A *promotora*-led educational intervention consisting of a 2-h group session focused on addressing common gaps in knowledge relating to breast and cervical cancer. Women were invited to attend an initial class and were also invited to attend a refresher class 1 yr later if they wished	Usual care. Women received a mailed reminder and a telephone call about breast and cervical cancer screening	Women in the intervention group were more likely to report having had a Pap test within the past 2 yr (OR, 2.8; 95% CI, 1.3–6.0). No significant differences were reported for having had a Pap test within the past 1 yr
Paskett et al. (2011) USA	RCT Women received 2 in-person home visits, 2 telephone calls, and 4 postcards from lay health advisors to educate them about cervical cancer, Pap test screening, and treatment, to provide individualized counselling, and to remind women to report for screening	Usual care. Women received a brochure and a letter from their physician	More women in the intervention group had had a Pap test by the end of the study compared with those randomized to usual care (51.1% vs 42.0%; OR, 1.44; 95% CI, 0.89–2.33). Self-report results were more pronounced (71.3% vs 54.2%; OR, 2.10; 95% CI, 1.22–3.61)
Byrd et al. (2013) USA	RCT Individual delivery of the AMIGAS programme consisted of a video novella and flip chart to inform women about barriers and facilitators to cervical cancer screening. Games and activities were also used, and *promotoras* were used to gauge women's interest in being screened and to help them move towards screening in a culturally tailored manner Three versions of the AMIGAS programme were tested: (i) the entire programme as described above, (ii) the programme without the video, and (iii) the programme without the flip chart	Usual care. No *promotora* education, but women might have been exposed to some education in clinics or in the media	52.3% of those in the full AMIGAS programme group and 24.8% of those in the control group reported being screened (*P* < 0.0001). There was no statistically significant difference in screening participation among the 3 intervention groups
Abiodun et al. (2014) Nigeria	Quasi-RCT Group health education on cervical cancer and screening (didactic lectures, movie, and participatory discussions)	Education on breast cancer and screening	The proportion of women who had undergone cervical screening increased from 4.3% to 8.3% (*P* = 0.038)
Dehdari et al. (2014) Islamic Republic of Iran	Quasi-RCT Weekly 60-min educational sessions provided to women in small groups for 4 wk	Usual care	Participation in screening increased from 0% to 61.9% in the intervention group vs from 0% to 10% in the control group (*P* < 0.05) 3 mo after intervention

Table 3.2 (continued)

Reference Country or territory	Study type Intervention	Control group	Key outcomes
Braun et al. (2015) USA	RCT Navigation services including outreach, education, making appointments, sending reminders, providing transportation to appointments, communicating with providers, and completing paperwork	Nutrition education and relevant cancer education materials from another health-care entity	57.0% of women in the intervention group and 36.4% of women in the control group had had a Pap test in the past 24 mo ($P = 0.001$)
Thompson et al. (2017) USA	RCT Group 1 (low-intensity): Participants were mailed a culturally appropriate, Spanish-language video about cervical cancer screening and how to access screening in their area Group 2 (high-intensity): Participants were visited at home by a *promotora* who showed them the education video, informed them of resources to reduce barriers to screening, answered questions, and helped them to make an appointment	Usual care. Participants had access to information about cervical cancer and Pap testing available from their health centre	7 mo after randomization, significantly more women in the high-intensity intervention group had had a Pap test (53.4%) than women in the low-intensity group (38.7%; $P < 0.001$) and the control group (34.0%; $P < 0.01$) The difference in participation between the control group and the low-intensity group was not significant ($P = 0.40$)

CI, confidence interval; GP, general practitioner; h, hour or hours; HR, hazard ratio; min, minute or minutes; mo, month or months; OR, odds ratio; RCT, randomized controlled trial; vs, versus; wk, week or weeks; yr, year or years.

women's participation, such as the style and tone of the letter, the actual service being offered, and who signs the letter. It is important to be aware that similar strategies can differ in ways that might affect participation, including the broader health and social policy environment, the health organization characteristics, and the specifics of the intervention. For example, in a cluster RCT in Denmark (Jensen et al., 2009), women in the intervention group received the usual invitation letter to the screening programme as well as a more targeted letter signed by their general practitioner (GP); this contributed to an increase in screening participation in the intervention group compared with the group who received only the usual invitation letter as standard of care (odds ratio [OR], 1.17; 95% CI, 1.04–1.30). In addition, the GPs of the women in the intervention group were visited by a facilitator who identified avenues for quality improvement and offered help with sending screening reminders to patients.

All the invitation strategies presented in Table 3.2 were found to increase screening participation in the intervention groups compared with the control groups, with the exception of the strategies used in the study by Adonis et al. (2017) in South Africa. Two studies evaluated the effect of using text messages to increase screening participation, with contradictory findings (Rashid et al., 2013; Firmino-Machado et al., 2018).

(b) Educational interventions

A meta-analysis of five RCTs in 1609 women evaluated the effect of educational interventions on participation in cervical cancer screening (Musa et al., 2017); it found that the use of theory-based educational interventions resulted in a more than 2-fold (OR, 2.46; 95% CI, 1.88–3.21) increase in screening participation in women who received cervical cancer education compared with women in the comparison group. Similarly, a systematic review of 17 RCTs and non-randomized studies (Agide et al., 2018) concluded that

health education interventions were effective in increasing participation rates after implementation, although the effectiveness varied with study setting, population characteristics, and mode of delivery.

Table 3.2 summarizes 12 RCTs that have evaluated the effect of educational interventions on cervical screening participation in non-attenders published since 2005 and conducted in the USA ($n = 9$), American Samoa ($n = 1$), the Islamic Republic of Iran ($n = 1$), and Nigeria ($n = 1$). Most studies reported an increase in screening participation in the intervention group compared with the control group, despite a wide variation in the educational modality evaluated: lay health worker outreach plus media education campaign (Mock et al., 2007), lay health worker outreach plus different forms of audiovisual support (Taylor et al., 2010; Byrd et al., 2013; Thompson et al., 2017), home visits by lay health workers plus invitation letters and postcards (Paskett et al., 2011), group education in different settings (Hiatt et al., 2008; Mishra et al., 2009; O'Brien et al., 2010; Nuño et al., 2011; Abiodun et al., 2014; Dehdari et al., 2014), and help with navigating the health service, including outreach, education, making appointments, sending reminders, providing transportation to appointments, communicating with health-care providers, and completing paperwork on services (Braun et al., 2015).

Only one study (Hiatt et al., 2008), which was conducted in multiethnic, underserved women in the San Francisco Bay Area, reported no difference in screening participation between the intervention group (which used an outreach strategy in which racially and ethnically diverse lay health workers were used to engage women) and the control group. [The authors noted that the high baseline screening participation of these women (> 85%) may have contributed to the difficulty of assessing the value of the intervention.]

(c) Strategies targeting health-care providers

Evidence presented in the 2005 *IARC Handbook* ([IARC, 2005](#)) was inconclusive with regard to the effect of strategies targeting health-care providers. An update of the evidence from studies in high-income countries published by the Community Preventive Services Task Force in the USA ([Sabatino et al., 2012](#)) concluded that there was sufficient evidence that provider assessment (evaluating provider performance in offering and/or delivering screening to clients) and feedback (presenting health-care providers with information about their performance in providing screening services) were effective in increasing cervical screening participation, and that there was insufficient evidence to determine the effectiveness of provider incentives in increasing cervical screening participation.

3.2.2 Interventions to increase participation in screening by HPV testing

This section summarizes evidence from studies that have evaluated participation in screening using self-collection of samples for HPV testing compared with Pap testing or with VIA. In addition, evidence is summarized from studies comparing screening participation in women with self-collected samples versus clinician-collected samples for HPV DNA-based testing.

(a) Self-collection of samples for HPV testing versus cytology-based screening

[Table 3.3](#) lists 28 studies that have evaluated the effect of using HPV self-sampling versus cytology-based screening as a strategy to increase participation in women who do not attend screening. These studies were carried out in Europe ($n = 21$), the USA ($n = 3$), Canada ($n = 2$), Australia ($n = 1$), and Mexico ($n = 1$). Most of the studies analysed the effect of mailing an invitation to use self-sampling (using opt-in or opt-out strategies), accompanied by different educational materials and support activities that were part of the invitation strategy. [Therefore, it cannot be ruled out that any positive effect on screening participation reported in those studies could be due in part to the effect of the accompanying materials.]

(i) Opt-in strategies

Under opt-in strategies, women request a self-sampling kit through some mechanism (a letter, a telephone call, or by picking it up at a specific location).

In a meta-analysis of 25 RCTs aiming to determine whether offering self-sampling kits to underscreened women generated higher participation rates compared with invitation or reminder letters, [Arbyn et al. (2018)](#) found that opt-in strategies in which women had to request a self-sampling kit were not more effective than invitation letters (relative participation, 1.22; 95% CI, 0.93–1.61). A separate meta-analysis by [Yeh et al. (2019)](#) similarly reported a non-significant increase in screening participation in women who requested an HPV self-sampling kit compared with women in the control group (cervical screening by cytology, VIA testing services, or clinician-collected primary HPV testing) (RR, 1.28; 95% CI, 0.90–1.82).

Seven of the studies included in [Table 3.3](#) evaluated the opt-in option ([Giorgi Rossi et al., 2011](#), [2015](#); [Broberg et al., 2014](#); [Ivanus et al., 2018](#); [Kellen et al., 2018](#); [Kitchener et al., 2018](#); [Tranberg et al., 2018](#)), and four of them showed increased screening participation in the intervention group compared with the control group. One study in Sweden found that an opt-in self-sampling strategy was more effective than the standard invitation protocol in increasing participation in women who do not attend screening, in the context of a national population-based screening programme, but only after a reminder was sent ([Broberg et al., 2014](#)) (RR, 2.32; 95% CI, 2.00–2.70). In the study by [Kellen et al. (2018)](#), women in the intervention group had the choice

Table 3.3 Studies on interventions to increase participation of women in screening using HPV self-sampling (2005–present)

Reference Country	Study type Intervention	Control group	Outcomes
Compared with cytology-based screening			
Bais et al. (2007) Netherlands	RCT An HPV self-sampling kit was mailed with written and illustrated instructions for use and a return envelope A telephone line for women who had questions about HPV and cervical cancer was made available to all women throughout the study	Women received a recall letter, inviting them for conventional cytology	Total screening participation in the intervention group was 34.2%. Screening participation in the control group was 17.6%. Participation in the intervention group was significantly higher ($P < 0.001$)
Gök et al. (2010) Netherlands	RCT Women received a cervicovaginal material collection kit	Women received a reminder to report for conventional cytology	The participation rate in the self-sampling group was significantly higher than that in the control group (crude, 26.6% vs 16.4%; $P < 0.001$; adjusted, 27.5% vs 16.6%; $P < 0.001$); 10.9% difference (95% CI, 6.5–15.3%; $P < 0.001$)
Giorgi Rossi et al. (2011) Italy	RCT (4 arms) Group 1: Women were offered the option of an HPV self-sampling kit (the sample to be sent back by mail or delivered to a clinic). The women had to call a toll-free telephone number to opt in Group 2: An HPV self-sampling kit was directly mailed to women. The package included an instruction package, background information on HPV and cervical cancer, the self-sampling device, and a prepaid pack to send the sample back	Invitation letter to (a) a Pap test or (b) an HPV test at a clinic	Inviting women through the standard recall letter had the same participation rate in both control groups (13.9% in Pap test group and 14.9% in HPV test group) Compared with standard recall (Pap test), intervention 2 increased participation (RR, 1.41; 95% CI, 1.10–1.82), but intervention 1 decreased participation (RR, 0.62; 95% CI, 0.45–0.86)
Lazcano-Ponce et al. (2011) Mexico	RCT HPV DNA self-sampling at home. Nurses visited women at home to provide them with HPV self-sampling kits and give instructions on how to use them. Women who could not be reached at home were reassigned to the cytology group	Referral to local clinic for Pap test	98% of women in the self-sampling group were screened vs 87% who attended a clinic for a Pap test ($P = 0.001$)
Virtanen et al. (2011) Finland	RCT Women were sent an HPV self-sampling kit, instructions, a brochure about HPV and cervical cancer, and a questionnaire. An information letter was sent to all women in this group a few weeks before the kits were sent	Women were sent a new letter inviting them for cervical screening as well as a brochure about HPV and cervical cancer	31.5% of women in the intervention group were screened vs 25.9% in the control group. Adjusted RR, 1.21 (95% CI, 1.13–1.30)

Table 3.3 (continued)

Reference Country	Study type Intervention	Control group	Outcomes
Wikström et al. (2011) Sweden	RCT Women were sent an information letter, followed a few days later by an HPV self-sampling kit, instructions for use, and a prepaid return envelope. This was provided free of charge. Women were given a reminder if they did not respond	Standard recall. Women were invited again for Pap test screening as part of the existing Pap test screening regime. These women had to pay 100 SEK (~€10) for the Pap test	39% of women in the intervention group were screened vs 9% in the control group ($P < 0.001$)
Piana et al. (2011) France	RCT Women were sent an information letter, followed 1 mo later by an HPV self-sampling kit (if they did not opt out), instructions for use, and a prepaid return envelope	Second invitation to cytology-based screening	Response to the second invitation to Pap testing was significantly lower (7.2%) than response to the self-sampling kit (26.4%) ($P < 0.001$)
Szarewski et al. (2011) England	RCT Women were sent a package with a contact letter, an information leaflet on HPV, an HPV self-sampling kit with instructions for use, and a prepaid return envelope	Standard recall. Women were sent a normal letter from their primary care trust inviting them for cervical cytology	Participation was 10.2% in the intervention group vs 4.5% in the control group ($P < 0.0001$)
Darlin et al. (2013) Sweden	RCT Women were sent an HPV self-sampling kit with instructions for use, a questionnaire, and a prepaid return envelope. If a woman did not respond within 1 mo, a second complete kit was sent	Flexible no-fee cytology screening appointments. If women did not respond, a second letter was sent with additional possible appointment times	In the intervention group, 14.7% of women returned a self-collected sample. In the control group, 4.2% were screened ($P < 0.0001$)
Sancho-Garnier et al. (2013) France	RCT Women were sent an initial letter outlining information about HPV and cervical cancer and explaining that an HPV self-sampling kit would soon be sent. The kit included the self-sampling device, instructions with illustrations, and a prepaid return envelope	Invitation for Pap test. Women were sent an invitation for Pap testing with a list of centres that perform screening	18.3% of women in the intervention group were screened vs 2.0% of women in the control group ($P < 0.001$)
Broberg et al. (2014) Sweden	RCT Group 1: Women were sent a letter inviting them to order an HPV self-sampling kit. The letter included information about HPV and screening. The women were also told the test kit would cost them €11. Those who agreed were sent a self-sampling kit and prepaid return envelope. Those who ordered a kit and did not return it were sent a reminder Group 2: Telephone contact by midwives, offering women appointments for Pap testing	Standard care. Women received annual invitations for Pap test screening	Participation was 24.5% in the HPV self-sampling group vs 18.0% in the telephone contact group vs 10.6% in the control group. RR compared with control group, 2.32 (95% CI, 2.00–2.70) and compared with telephone contact group, 1.36 (95% CI, 1.19–1.57)

Table 3.3 (continued)

Reference Country	Study type Intervention	Control group	Outcomes
Haguenoer et al. (2014) France	RCT Group 1: Women were sent an HPV self-sampling kit, an invitation letter to provide a specimen, an information leaflet, a questionnaire, and a prepaid return envelope Group 2: Women were sent a recall letter, inviting them for Pap testing	No intervention	22.5% of women in the self-sampling group, 11.7% in the recall letter group, and 9.9% in the control group were screened. Participation in the self-sampling group was significantly higher compared with both the recall letter group (OR, 2.20; 95% CI, 1.85–2.62) and the control group (OR, 2.64; 95% CI, 2.21–3.17). There was no significant difference between the recall and control groups (OR, 1.20; 95% CI, 0.98–1.47)
Sewali et al. (2015) USA	Pilot RCT Women were given an HPV self-sampling kit during information sessions, along with instructions that were translated and tailored for the Somali community. Participants were given a telephone number to call with questions they may have had related to self-sampling. Participants were requested to return their specimen to a CHW within 3 mo of receiving the self-sampling kit	Standard of care. Women were asked to attend their usual clinic for Pap test screening	65.6% of women in the intervention group were screened vs 19.4% of women in the control group (OR, 14.18; 95% CI, 2.73–73.51; $P = 0.002$)
Giorgi Rossi et al. (2015) Italy	RCT Group 1: HPV self-sampling kit mailed to women at home. This kit included the sampler, instructions, information on cervical cancer and prevention, and a return envelope. Women were sent an explanatory letter 1 wk before the kits were sent Group 2: Women were sent a letter inviting them to pick up an HPV self-sampling kit at a designated pharmacy in their area. This letter was accompanied by information on cervical cancer and prevention	Standard recall letter inviting women for Pap test and/or HPV screening in a clinic. Choice of screening was dependent on the local health authority	21.6% of women in the intervention 1 group were screened vs 11.9% in the control group (RR, 2.01; 95% CI, 1.3–3.1). The pharmacy pickup group (12.0% participation) had a participation similar to that of the control group (RR, 1.01; 95% CI, 0.62–1.66)
Cadman et al. (2015) England	Pragmatic RCT Mailed HPV self-sampling kit, with instructions	Women received an invitation letter inviting them for standard cervical cytology screening	13% of women in the intervention group underwent some form of screening (8% returned a self-collected sample, and 5% attended for cytology); 6% of women in the control group responded to a further invitation for cervical screening (RR, 2.25; 95% CI, 1.90–2.65)

Table 3.3 (continued)

Reference Country	Study type Intervention	Control group	Outcomes
Enerly et al. (2016) Norway	RCT Women were sent an explanatory letter; 3 wk later they were sent an HPV self-sampling kit with instructions for use and a prepaid return envelope	Standard of care; a second reminder letter was sent	Total participation was 33.4% in the intervention group vs 23.2% in the control group (RR, 1.44; 95% CI, 1.28–1.62)
Zehbe et al. (2016) Canada	Community RCT Women were offered HPV self-sampling by community-based research assistants after an educational event and other recruitment efforts. The initial 3-mo phase of the trial was followed by a 1–2-mo break. Women in both groups were then offered the alternative screening strategy	Women were offered Pap testing by community-based research assistants after an educational event and other recruitment efforts	In the initial phase of the trial, HPV self-sampling participation in the intervention group was 20.0%. In the control group, Pap testing participation was 14.3%. This is a non-significant difference After the second phase in which the alternative screening method was offered, the cumulative participation in screening was 20.6% in the intervention group and 16.0% in the control group. This is a non-significant difference
Racey et al. (2016) Canada	Pragmatic randomized intervention study Group 1: Women were sent an explanatory letter from their clinic, which was followed 2 wk later (if they did not opt out) by an HPV self-sampling kit, information on HPV and cervical cancer, instructions for self-sampling, and a prepaid return envelope. Those who did not respond within 1 mo of receiving the self-sampling kit received a reminder telephone call Group 2: Women were sent an invitation letter for scheduling a Pap test plus information on HPV and cervical cancer. If no response was recorded within 1 mo, a reminder telephone call was made	Standard of care opportunistic screening	In the control group, 8.6% of women underwent opportunistic Pap test screening; 32% of women in the intervention 1 group were screened and 15.4% of women in the intervention 2 group. Compared with the control group, women who received the self-sampling kit (intervention 1) were 3.7 (95% CI, 2.2–6.4) times as likely to undergo screening; women in the cytology group (intervention 2) were 1.8 (95% CI, 1.0–3.2) times as likely to undergo screening
Sultana et al. (2016) Australia	RCT Women were sent a pre-invitation letter, allowing them 3 wk to opt out of receiving a self-sampling kit. After 3 wk, women were sent an HPV self-sampling kit, instructions for its use, information on HPV and cervical cancer, a personal information form, and a prepaid return envelope for their specimen and form	Standard invitation letter. Women received a letter inviting them for Pap test screening, a personal information form, and a return envelope to return their information form	20.3% of women in the intervention group participated in screening vs 6.0% of those in the control group (P < 0.001) Participation was 11.5% vs 6.4% for never-screened women (P < 0.001)

Table 3.3 (continued)

Reference Country	Study type Intervention	Control group	Outcomes
Viviano et al. (2017) Switzerland	RCT Women received a self-sampling kit, instructions for use at home, and a prepaid return envelope	Women received an invitation letter for cytology-based screening	92.7% of women in the control group underwent screening and 94.3% in the intervention group. Differences in screening participation were not statistically significant
Carrasquillo et al. (2018) USA	Single-blind randomized pragmatic clinical trial Group 1 (outreach): Women were provided with a brochure in their preferred language about cervical cancer and how they can get screened in their local community Group 2 (navigation): Outreach as in the intervention 1 group, plus they were scheduled a 30-min one-on-one session with a CHW to help with appointments, navigate challenges, and follow up Group 3 (self-sampling): Same as groups 1 and 2, but during their educational session with the CHW women were given the option of HPV self-sampling	NA	At 6 mo, women in the self-sampling option group were significantly more likely to report having had screening than women in the outreach group (77.3% vs 31.3%, OR, 7.47; 95% CI, 4.75–11.73). Women in the navigation group were also significantly more likely to report having had screening compared with women in the outreach group (42.5% vs 31.3%; OR, 1.62; 95% CI, 1.07–2.45). The proportion of women screened in the self-sampling group was also significantly higher than the proportion screened in the navigation group (OR, 4.61; 95% CI, 3.02–7.05)
Gustavsson et al. (2018) Sweden	Randomized study Mailed HPV self-sampling kit. Women were sent an invitation, a sampling brush, an FTA card, instructions for use, and a prepaid return envelope. Women who did not respond within 3 wk were sent a reminder	Standard of care. Invitation to the regional cervical cancer screening programme, which involves Pap testing conducted by a midwife	The screening participation in the intervention group was higher than that in the control group (47% vs 39%; $P < 2.2 \times 10^{-16}$)
Ivanus et al. (2018) Slovenia	Open-label, multiarm study with a randomized design Group 1 (opt-in HPV self-collection): Women were sent a package informing them they were late for screening and inviting them to order a self-sampling kit or schedule an appointment with their gynaecologist for cytology screening Group 2 (opt-out): Women were mailed a note that they were late for screening and that a self-sampling device would be sent directly to them in the next 2 wk if they did not opt out	Women were sent an information package, informing them that they were late for screening and inviting them to make an appointment with their gynaecologist	Compared with the control group (18.4%), the opt-out group had the highest participation (37.7%) (RR, 2.0; 95% CI, 1.9–2.2), followed by the opt-in group (34.0%) (RR, 1.8; 95% CI, 1.7–2.0)

Table 3.3 (continued)

Reference Country	Study type Intervention	Control group	Outcomes
Kellen et al. (2018) Belgium	Parallel, RCT (4 arms) Group 1 (opt-out): Women were sent a package by mail including information, a self-sampling kit, instructions, and a prepaid return envelope Group 2 (opt-in): Women were mailed an information package and a letter offering the opportunity to order a self-sampling kit	Control 1: Women were sent the standard recall letter, inviting them to attend for a Pap test with their GP or gynaecologist Control 2: No intervention	25.8% of the women in the opt-out group (OR, 3.2; 95% CI, 3.0–3.5) and 18.7% of the women in the opt-in group (RR, 2.3; 95% CI, 2.2–2.5) were screened within 1 yr In the control groups, 10.5% of the women who received a standard recall letter and 8% of those who received no intervention had a Pap test within 1 yr
Kitchener et al. (2018) United Kingdom	Cluster RCT Group 1: Mailed HPV self-sampling kit Group 2: Opt-in for HPV self-sampling Group 3: Choice between nurse navigator assistance and HPV self-sampling	Standard care; invitation for first cervical screening	Compared with standard care, mailed self-sampling kits resulted in an increase in screening participation over 12 mo (OR, 1.51; 95% CI, 1.20–1.91), but the opt-in approach had no effect (OR, 1.07; 95% CI, 0.87–1.33)
Tranberg et al. (2018) Denmark	Randomized, controlled-effectiveness, population-based trial Group 1 (opt-out): Women were directly mailed a reminder, an information package, an HPV self-sampling kit, and a prepaid return envelope. They could report to a clinic for standard cytology Group 2 (opt-in): Women received the same package as the opt-out group except for the self-sampling kit. They were also given information about how to order a self-sampling kit by email, text message, telephone, or through a webpage	Standard reminder letter inviting women for screening with their GP	Compared with participation in the control group (25.2%), participation was significantly higher in the directly mailed group (38.0%; RR, 1.51; 95% CI, 1.40–1.62) and in the opt-in group (30.9%; RR, 1.23; 95% CI, 1.13–1.32)
Winer et al. (2019) USA	RCT Women received usual care plus a mailed HPV self-sampling kit with self-sampler, instructions, information letter, and prepaid return envelope. If a woman did not return a sample or opt out within 3 wk, staff delivered up to 3 reminder telephone calls. Because HPV self-sampling is not the standard of care in the USA, the information letter advised women to report for Pap test screening even if they participated in self-sampling	Usual care. Outreach to women to attend for screening, and clinicians were issued alerts that women were overdue for screening	26.3% of women in the intervention group received screening vs 17.4% in the control group (RR, 1.51; 95% CI, 1.43–1.60)

Table 3.3 (continued)

Reference Country	Study type Intervention	Control group	Outcomes
Peeters et al. (2020) Belgium	RCT Women were offered an HPV self-sampling kit at their GP practice along with instructions for use. They could collect the sample at home and mail it using a prepaid envelope or return it to their GP	Women were encouraged by their GP to make an appointment for Pap testing	Screening participation was 78% in the intervention group and 51% in the control group. Adjusted OR, 3.41 (95% CI, 1.31–8.87)
Compared with VIA			
Moses et al. (2015) Uganda	Pilot RCT Group 1 (HPV self-sampling): Outreach workers visited women at home or their place of work and provided them with a Dacron swab and instructions and asked them to provide self-collected samples for carcinogenic HPV DNA testing. Women were asked to take the sample immediately and return it to the outreach worker Group 2 (VIA): Outreach workers visited women at home or at their place of work and invited them to attend a clinic for a scheduled appointment for VIA using a see-and-treat approach		48.4% of women in the VIA group were screened vs 99.2% in the HPV self-collection group (*P* < 0.001)
Gizaw et al. (2019) Ethiopia	Cluster RCT HPV self-sampling after a sensitization programme that provided information about cervical cancer and screening. Women were offered an HPV self-sampling kit and performed self-collection under the supervision of a trained health professional at a health facility	Hospital-based VIA after a sensitization programme that provided information about cervical cancer and screening and support to schedule an appointment by a trained nurse	84.1% of women in the HPV self-sampling group were screened vs 50.5% in the VIA group (*P* < 0.0001)
Compared with HPV testing (clinician-collected HPV testing or alternative offer of self-collection)			
Arrossi et al. (2015b) Argentina	Cluster RCT CHWs offered women HPV self-sampling testing during a routine home visit. Women were provided with education on HPV self-sampling	CHWs encouraged women to seek HPV testing at any provincial health centre	86% of women in the intervention group had any HPV test within 6 mo of the CHW visit, compared with 20% in the control group (RR, 4.02; 95% CI, 3.44–4.71)
Modibbo et al. (2017) Nigeria	Community-based RCT Women were given dry flocked swabs for HPV DNA self-sampling and prepaid return envelopes. They had the option to mail the envelope, drop it off at certain points in the community, or return it to the central hospital	Women were given appointments for hospital-based HPV DNA testing	92.5% of women in the intervention group completed screening vs 56.5% in the control group (*P* < 0.001)

Table 3.3 (continued)

Reference Country	Study type Intervention	Control group	Outcomes
Huchko et al. (2018) Kenya	Two-phase cluster RCT HPV self-sampling offered though periodic community health campaigns; outreach and mobilization were included	HPV self-sampling offered at government health facilities. Women were provided with the same information and instructions as those in the intervention	60.0% of women in the intervention group self-collected a sample vs 37.0% of women in the control group ($P < 0.001$)
Kobetz et al. (2018) USA	Randomized pragmatic trial A CHW provided women with education about cervical cancer and instructions on how to perform self-sampling at a community location in-person. Women had the option to give the self-collected sample directly to the CHW or to mail their sample later	Women were sent a self-sampling kit that included a prepaid return envelope and instructions for how to use the kit. CHWs telephoned women to ensure they had received their kit and to provide health education about cervical cancer	In the mailed HPV self-sampling kit groups, 71.6% of women returned a sample; in the CHW-provided self-sampling group, 81.0% of women returned a sample ($P < 0.01$)

CHW, community health worker; CI, confidence interval; FTA, Flinders Technology Associates; GP, general practitioner; HPV, human papillomavirus; mo, month or months; NA, not applicable; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; VIA, visual inspection with acetic acid; vs, versus; wk, week or weeks; yr, year or years.

between either self-sampling or attending for screening with the Pap test at a health clinic. The opt-in self-sampling strategy significantly increased screening participation compared with an invitation letter for Pap-based screening, but only when total participation (self-sampling and cytology screening) was computed in the intervention arm, which suggests that factors related to the invitation strategy might have prompted women to get screened irrespective of the chosen method.

(ii) Mailed with opt-out option

A meta-analysis performed in 2018 showed that mailing self-sampling kits to women at their home address generated higher response rates compared with invitations or reminder letters to attend conventional cytology screening or HPV testing, or both, with the sample collected by a clinician (pooled relative participation, 2.33; 95% CI, 1.86–2.91) (Arbyn et al., 2018). Similar results were found in the meta-analysis by Yeh et al. (2019), which reported greater screening participation in HPV self-sampling when self-sampling kits were mailed directly to women at their home address (RR, 2.27; 95% CI, 1.89–2.71) compared with women in the control group (cervical screening by cytology, VIA testing services, or clinician-collected primary HPV testing). This increased participation was reported by both meta-analyses, despite significant heterogeneity across the studies in terms of the strategy offered and the population characteristics.

Studies in Table 3.3 that evaluated the opt-out approach included: written or illustrated instructions for use and a return envelope or packaging (Bais et al., 2007; Cadman et al., 2015; Viviano et al., 2017; Kitchener et al., 2018), written instructions and background information on HPV and cervical cancer and a return envelope (Giorgi Rossi et al., 2011; Szarewski et al., 2011; Haguenoer et al., 2014; Kellen et al., 2018; Tranberg et al., 2018), instructions and information about HPV and cervical cancer

and an information letter before sending of the self-sampling kits (Gök et al., 2010; Piana et al., 2011; Virtanen et al., 2011; Wikström et al., 2011; Sancho-Garnier et al., 2013; Giorgi Rossi et al., 2015; Enerly et al., 2016; Sultana et al., 2016; Ivanus et al., 2018), all of the above and a second complete kit sent to non-responders (Darlin et al., 2013) or a reminder telephone call or letter (Racey et al., 2016; Gustavsson et al., 2018; Winer et al., 2019) or a telephone call by community health workers to ensure the women received their kits and to provide health education about cervical cancer (Kobetz et al., 2018).

(iii) HPV self-sampling kits offered by GPs

In one study in Belgium (Peeters et al., 2020), HPV self-sampling kits offered to women by their GP, along with instructions for their use at home, increased screening participation compared with encouragement by the GP to make an appointment for cytology-based screening by a GP of the practice or a gynaecologist of choice (RR, 3.41; 95% CI, 1.31–8.87). Women collected the sample at home and could either mail it to the laboratory using a prepaid envelope or return it to their GP's practice.

(iv) HPV self-sampling kits offered through outreach strategies

Studies comparing screening with HPV self-sampling offered through outreach strategies versus clinic-based Pap testing (control group) included one study in Canada (Zehbe et al., 2016), one in Mexico (Lazcano-Ponce et al., 2011), and two in the USA (Sewali et al., 2015; Carrasquillo et al., 2018; Table 3.3). In both studies in the USA, women in the intervention (self-sampling) group were significantly more likely to have been screened compared with those in the control group (Sewali et al., 2015: OR, 14.18; 95% CI, 2.73–73.51; Carrasquillo et al., 2018: OR, 7.47; 95% CI, 4.75–11.73). In the study by Carrasquillo et al. (2018), screening participation was higher in the self-sampling group

than in the outreach and navigation groups, suggesting that when compared with cytology-based screening, HPV self-sampling has an impact on screening participation even when the effects of outreach activities have been controlled for.

In the study in Mexico (Lazcano-Ponce et al., 2011), a small difference in screening participation was observed (98% in the intervention group vs 87% in the control group; *P* = 0.001). [Because the main objective of the study was to evaluate the effectiveness of self-sampling to diagnose cervical intraepithelial neoplasia, it is possible that additional outreach might have been carried out in the cytology-based screening arm, with potential underestimation of the impact of self-sampling.]

(b)   Self-collection of samples for HPV testing versus VIA

Two studies in sub-Saharan Africa compared screening participation in women using HPV self-sampling and in women attending a clinic for VIA (Moses et al., 2015; Gizaw et al., 2019; Table 3.3). In a study in Uganda (Moses et al., 2015), women in one group performed self-sampling at home or at their workplace, and women in the other group were invited to attend a health clinic to undergo VIA and were reminded by telephone the day before their scheduled visit. In a study in Ethiopia (Gizaw et al., 2019), women were either offered self-sampling at home or given a choice of appointment days to attend for VIA. In both studies, women in the VIA arm had lower screening participation: 48.4% in the VIA arm and 99.2% in the HPV self-sampling arm (Moses et al., 2015) and 50.5% in the VIA arm and 84.1% in the HPV self-sampling arm (Gizaw et al., 2019).

(c)   Self-collected versus clinician-collected samples for HPV testing

Three studies evaluated screening participation in women using HPV self-sampling compared with women who had samples collected by a clinician for HPV testing (Arrossi et al., 2015b; Giorgi Rossi et al., 2015; Modibbo et al., 2017; Table 3.3). In a community-based randomized trial involving 400 women in a semi-urban district of Abuja, Nigeria, participation in screening was higher in those offered HPV self-sampling during a community gathering compared with those offered clinician-collected HPV testing (92.5% vs 56.5%; *P* < 0.001) (Modibbo et al., 2017). In a population-based cluster-randomized trial in 6013 women in the province of Jujuy, Argentina, involving community health worker outreach, screening participation in the self-sampling arm was significantly higher than for clinician-collected HPV samples (RR, 4.02; 95% CI, 3.44–4.71) (Arrossi et al., 2015b). A multicentre RCT in six local health authorities in Italy involving 14 041 women (Giorgi Rossi et al., 2015) compared mailing of self-sampling kits, pharmacy pick-up of self-sampling kits, and standard recall at health clinics using HPV-based screening (clinician-collected sampling, in four centres) or cytology-based screening (in three centres). Compared with participation rates in women who were mailed self-sampling kits, screening participation was lower in three of the clinician-collected HPV-testing sites; no difference in screening participation was observed at a fourth centre. [The heterogeneity among centres suggests that there are strong effect modifiers not only at cultural and social levels, but also linked to the logistics and organization of the intervention and clinics.] A quasi-experimental before-and-after analysis comparing two periods – a cytology-based screening period (2010–2011) and an HPV-based screening period (2012–2014) (Arrossi et al., 2019) – showed similar screening participation in the periods (52.7% for the

cytology period and 53.2% for the HPV period) only when both self-collected and clinician-collected samples were included.

(d) Comparison between self-sampling offered through health centres and in community settings

Two studies evaluated the effectiveness of various programmes using different methods to offer HPV self-sampling (Table 3.3). In a cluster-randomized trial conducted in 12 communities in western Kenya and involving 4944 women (Huchko et al., 2018), HPV self-sampling offered though periodic community health campaigns yielded higher screening participation rates compared with HPV self-sampling offered at government health facilities (60.0% vs 37.0%; *P* < 0.001). A study in Florida, USA, in 600 women found that HPV self-sampling offered in-person by community health workers in community settings resulted in higher screening participation compared with self-sampling delivered by mail (81.0% vs 71.6%; *P* < 0.01) (Kobetz et al., 2018).

References

Abiodun OA, Olu-Abiodun OO, Sotunsa JO, Oluwole FA (2014). Impact of health education intervention on knowledge and perception of cervical cancer and cervical screening uptake among adult women in rural communities in Nigeria. *BMC Public Health*. 14(1):814. doi:10.1186/1471-2458-14-814 PMID:25103189

Acera A, Manresa JM, Rodriguez D, Rodriguez A, Bonet JM, Trapero-Bertran M, et al. (2017). Increasing cervical cancer screening coverage: a randomised, community-based clinical trial. *PLoS One*. 12(1):e0170371. doi:10.1186/1471-2458-14-814 PMID:25103189

Adonis L, Paramanund J, Basu D, Luiz J (2017). Framing preventive care messaging and cervical cancer screening in a health-insured population in South Africa: implications for population-based communication? *J Health Psychol*. 22(11):1365–75. doi:10.1177/1359105316628735 PMID:26888327

Adunlin G, Cyrus JW, Asare M, Sabik LM (2019). Barriers and facilitators to breast and cervical cancer screening among immigrants in the United States. *J Immigr Minor Health*. 21(3):606–58. doi:10.1007/s10903-018-0794-6 PMID:30117005

Agide FD, Garmaroudi G, Sadeghi R, Shakibazadeh E, Yaseri M, Koricha ZB, et al. (2018). A systematic review of the effectiveness of health education interventions to increase cervical cancer screening uptake. *Eur J Public Health*. 28(6):1156–62. doi:10.1093/eurpub/cky197 PMID:30346504

Akinyemiju TF (2012). Socio-economic and health access determinants of breast and cervical cancer screening in low-income countries: analysis of the World Health Survey. *PLoS One*. 7(11):e48834. doi:10.1371/journal.pone.0048834 PMID:23155413

Araujo M, Franck J-E, Cadot E, Gautier A, Chauvin P, Rigal L, et al. (2017). Contextual determinants of participation in cervical cancer screening in France, 2010. *Cancer Epidemiol*. 48:117–23. doi:10.1016/j.canep.2017.04.014 PMID:28482191

Arbyn M, Smith SB, Temin S, Sultana F, Castle P; Collaboration on Self-Sampling and HPV Testing (2018). Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. *BMJ*. 363:k4823. doi:10.1136/bmj.k4823 PMID:30518635

Arrossi S, Almonte M, Herrero R, Gago J, Sánchez Antelo V, Szwarc L, et al. (2020). Psycho-social impact of positive human papillomavirus testing in Jujuy, Argentina results from the Psycho-Estampa study. *Prev Med Rep*. 18:101070. doi:10.1016/j.pmedr.2020.101070 PMID:32257775

Arrossi S, Paolino M, Laudi R, Gago J, Campanera A, Marín O, et al. (2019). Programmatic human papillomavirus testing in cervical cancer prevention in the Jujuy Demonstration Project in Argentina: a population-based, before-and-after retrospective cohort study. *Lancet Glob Health*. 7(6):e772–83. doi:10.1016/S2214-109X(19)30048-8 PMID:31097279

Arrossi S, Paolino M, Sankaranarayanan R (2010). Challenges faced by cervical cancer prevention programs in developing countries: a situational analysis of program organization in Argentina. *Rev Panam Salud Publica*. 28(4):249–57. doi:10.1590/S1020-49892010001000003 PMID:21152712

Arrossi S, Paolino M, Thouyaret L, Laudi R, Campanera A (2017). Evaluation of scaling-up of HPV self-collection offered by community health workers at home visits to increase screening among socially vulnerable under-screened women in Jujuy Province, Argentina. *Implement Sci*. 12(1):17. doi:10.1186/s13012-017-0548-1 PMID:28193227

Arrossi S, Ramos S, Straw C, Thouyaret L, Orellana L (2016). HPV testing: a mixed-method approach to understand why women prefer self-collection in a middle-income country. *BMC Public Health*. 16(1):832. doi:10.1186/s12889-016-3474-2 PMID:27538390

Arrossi S, Thouyaret L, Herrero R, Campanera A, Magdaleno A, Cuberli M, et al.; EMA Study team (2015b). Effect of self-collection of HPV DNA offered by community health workers at home visits on uptake of screening for cervical cancer (the EMA study): a population-based cluster-randomised trial. *Lancet Glob Health*. 3(2):e85–94. doi:10.1016/S2214-109X(14)70354-7 PMID:25617202

Arrossi S, Thouyaret L, Laudi R, Marín O, Ramírez J, Paolino M, et al. (2015a). Implementation of HPV-testing for cervical cancer screening in programmatic contexts: the Jujuy demonstration project in Argentina. *Int J Cancer*. 137(7):1709–18. doi:10.1002/ijc.29530 PMID:25807897

Bacal V, Blinder H, Momoli F, Wu KY, McFaul S (2019). Is immigrant status associated with cervical cancer screening among women in Canada? Results from a cross-sectional study. *J Obstet Gynaecol Can*. 41(6):824–831.e1. doi:10.1016/j.jogc.2018.07.010 PMID:30361160

Bais AG, van Kemenade FJ, Berkhof J, Verheijen RHM, Snijders PJF, Voorhorst F, et al. (2007). Human papillomavirus testing on self-sampled cervicovaginal brushes: an effective alternative to protect nonresponders in cervical screening programs. *Int J Cancer*. 120(7):1505–10. doi:10.1002/ijc.22484 PMID:17205514

Barbadoro P, Ricciardi A, Di Tondo E, Vallorani S, Mazzarini G, Prospero E (2015). Utilization patterns of cervical cancer screening in Italy. *Eur J Cancer Prev*. 24(2):135–40. doi:10.1097/CEJ.0000000000000068 PMID:24977627

Bou-Orm IR, Sakr RE, Adib SM (2018). Cervical cancer screening among Lebanese women. *Rev Epidemiol Sante Publique*. 66(1):1–6. doi:10.1016/j.respe.2017.10.004 PMID:29249573

Brandão M, Tulsidás S, Damasceno A, Silva-Matos C, Carrilho C, Lunet N (2019). Cervical cancer screening uptake in women aged between 15 and 64 years in Mozambique. *Eur J Cancer Prev*. 28(4):338–43. doi:10.1097/CEJ.0000000000000459 PMID:30020115

Braun KL, Thomas WL Jr, Domingo JL, Allison AL, Ponce A, Haunani Kamakana P, et al. (2015). Reducing cancer screening disparities in Medicare beneficiaries through cancer patient navigation. *J Am Geriatr Soc*. 63(2):365–70. doi:10.1111/jgs.13192 PMID:25640884

Broberg G, Gyrd-Hansen D, Miao Jonasson J, Ryd ML, Holtenman M, Milsom I, et al. (2014). Increasing participation in cervical cancer screening: offering a HPV self-test to long-term non-attendees as part of RACOMIP, a Swedish randomized controlled trial. *Int J Cancer*. 134(9):2223–30. doi:10.1002/ijc.28545 PMID:24127304

Broberg G, Wang J, Östberg A-L, Adolfsson A, Nemes S, Sparén P, et al. (2018). Socio-economic and demographic determinants affecting participation in the Swedish cervical screening program: a population-based case-control study. *PLoS One*. 13(1):e0190171. doi:10.1371/journal.pone.0190171 PMID:29320536

Brousseau EC, Ahn S, Matteson KA (2019). Cervical cancer screening access, outcomes, and prevalence of dysplasia in correctional facilities: a systematic review. *J Womens Health (Larchmt)*. 28(12):1661–9. doi:10.1089/jwh.2018.7440 PMID:30939063

Buehler JW, Castro JC, Cohen S, Zhao Y, Melly S, Moore K (2019). Personal and neighborhood attributes associated with cervical and colorectal cancer screening in an urban African American population. *Prev Chronic Dis*. 16:E118. doi:10.5888/pcd16.190030 PMID:31469069

Byrd TL, Wilson KM, Smith JL, Coronado G, Vernon SW, Fernandez-Esquer ME, et al. (2013). AMIGAS: a multicity, multicomponent cervical cancer prevention trial among Mexican American women. *Cancer*. 119(7):1365–72. doi:10.1002/cncr.27926 PMID:23280399

Cadman L, Wilkes S, Mansour D, Austin J, Ashdown-Barr L, Edwards R, et al. (2015). A randomized controlled trial in non-responders from Newcastle upon Tyne invited to return a self-sample for human papillomavirus testing versus repeat invitation for cervical screening. *J Med Screen*. 22(1):28–37. doi:10.1177/0969141314558785 PMID:25403717

Carrasquillo O, Seay J, Amofah A, Pierre L, Alonzo Y, McCann S, et al. (2018). HPV self-sampling for cervical cancer screening among ethnic minority women in South Florida: a randomized trial. *J Gen Intern Med*. 33(7):1077–83. doi:10.1007/s11606-018-4404-z PMID:29594933

Chorley AJ, Marlow LA, Forster AS, Haddrell JB, Waller J (2017). Experiences of cervical screening and barriers to participation in the context of an organised programme: a systematic review and thematic synthesis. *Psychooncology*. 26(2):161–72. doi:10.1002/pon.4126 PMID:27072589

Chumworathayi B, Yuenyao P, Luanratanakorn S, Pattamadilok J, Chalapati W, Na-Nhongkai C (2007). Can an appointment-letter intervention increase Pap smear screening in Samliem, Khon Kaen, Thailand? *Asian Pac J Cancer Prev*. 8(3):353–6. PMID:18159966

Connolly D, Hughes X, Berner A (2020). Barriers and facilitators to cervical cancer screening among transgender men and non-binary people with a cervix: a systematic narrative review. *Prev Med*. 135:106071. doi:10.1016/j.ypmed.2020.106071 PMID:32243938

Darlin L, Borgfeldt C, Forslund O, Hénic E, Hortlund M, Dillner J, et al. (2013). Comparison of use of vaginal HPV self-sampling and offering flexible appointments as strategies to reach long-term non-attending women in organized cervical screening. *J Clin Virol*. 58(1):155–60. doi:10.1016/j.jcv.2013.06.029 PMID:23867008

de Jonge E, Cloes E, Op de Beeck L, Adriaens B, Lousbergh D, Orye GG, et al. (2008). A quasi-randomized trial on the effectiveness of an invitation letter to improve

participation in a setting of opportunistic screening for cervical cancer. *Eur J Cancer Prev.* 17(3):238–42. doi:10.1097/CEJ.0b013e3282b6fe2e PMID:18414195

Dehdari T, Hassani L, Hajizadeh E, Shojaeizadeh D, Nedjat S, Abedini M (2014). Effects of an educational intervention based on the protection motivation theory and implementation intentions on first and second Pap test practice in Iran. *Asian Pac J Cancer Prev.* 15(17):7257–61. doi:10.7314/APJCP.2014.15.17.7257 PMID:25227824

Dhendup T, Tshering P (2014). Cervical cancer knowledge and screening behaviors among female university graduates of year 2012 attending national graduate orientation program, Bhutan. *BMC Womens Health.* 14(1):44. doi:10.1186/1472-6874-14-44 PMID:24618416

Dieng M, Trevena L, Turner RM, Wadolowski M, McCaffery K (2013). What Australian women want and when they want it: cervical screening testing preferences, decision-making styles and information needs. *Health Expect.* 16(2):177–88. doi:10.1111/j.1369-7625.2011.00707.x PMID:21726363

Dietrich AJ, Tobin JN, Cassells A, Robinson CM, Greene MA, Sox CH, et al. (2006). Telephone care management to improve cancer screening among low-income women: a randomized, controlled trial. *Ann Intern Med.* 144(8):563–71. doi:10.7326/0003-4819-144-8-200604180-00006 PMID:16618953

Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, et al.; International Patient Decision Aids Standards (IPDAS) Collaboration (2006). Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. *BMJ.* 333(7565):417. doi:10.1136/bmj.38926.629329.AE PMID:16908462

Enerly E, Bonde J, Schee K, Pedersen H, Lönnberg S, Nygård M (2016). Self-sampling for human papillomavirus testing among non-attenders increases attendance to the Norwegian Cervical Cancer Screening Programme. *PLoS One.* 11(4):e0151978. doi:10.1371/journal.pone.0151978 PMID:27073929

Everett T, Bryant A, Griffin MF, Martin-Hirsch PP, Forbes CA, Jepson RG (2011). Interventions targeted at women to encourage the uptake of cervical screening. *Cochrane Database Syst Rev.* (5):CD002834. doi:10.1002/14651858.CD002834.pub2 PMID:21563135

Firmino-Machado J, Varela S, Mendes R, Moreira A, Lunet N, SCAN-Cervical Cancer collaborators (2018). Stepwise strategy to improve cervical cancer screening adherence (SCAN-Cervical Cancer) – automated text messages, phone calls and reminders: population based randomized controlled trial. *Prev Med.* 114:123–33. doi:10.1016/j.ypmed.2018.06.004 PMID:29894717

Gakidou E, Nordhagen S, Obermeyer Z (2008). Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. *PLoS Med.* 5(6):e132. doi:10.1371/journal.pmed.0050132 PMID:18563963

Giorgi Rossi P, Fortunato C, Barbarino P, Boveri S, Caroli S, Del Mistro A, et al.; HPV Self-sampling Italian Working Group (2015). Self-sampling to increase participation in cervical cancer screening: an RCT comparing home mailing, distribution in pharmacies, and recall letter. *Br J Cancer.* 112(4):667–75. doi:10.1038/bjc.2015.11 PMID:25633037

Giorgi Rossi P, Marsili LM, Camilloni L, Iossa A, Lattanzi A, Sani C, et al.; Self-Sampling Study Working Group (2011). The effect of self-sampled HPV testing on participation to cervical cancer screening in Italy: a randomised controlled trial (ISRCTN96071600). *Br J Cancer.* 104(2):248–54. doi:10.1038/sj.bjc.6606040 PMID:21179038

Gizaw M, Teka B, Ruddies F, Abebe T, Kaufmann AM, Worku A, et al. (2019). Uptake of cervical cancer screening in Ethiopia by self-sampling HPV DNA compared to visual inspection with acetic acid: a cluster randomized trial. *Cancer Prev Res (Phila).* 12(9):609–16. doi:10.1158/1940-6207.CAPR-19-0156 PMID:31337647

Gök M, Heideman DAM, van Kemenade FJ, Berkhof J, Rozendaal L, Spruyt JWM, et al. (2010). HPV testing on self collected cervicovaginal lavage specimens as screening method for women who do not attend cervical screening: cohort study. *BMJ.* 340(7752):c1040. doi:10.1136/bmj.c1040 PMID:20223872

Goss PE, Lee BL, Badovinac-Crnjevic T, Strasser-Weippl K, Chavarri-Guerra Y, St Louis J, et al. (2013). Planning cancer control in Latin America and the Caribbean. *Lancet Oncol.* 14(5):391–436. doi:10.1016/S1470-2045(13)70048-2 PMID:23628188

Gustavsson I, Aarnio R, Berggrund M, Hedlund-Lindberg J, Strand AS, Sanner K, et al. (2018). Randomised study shows that repeated self-sampling and HPV test has more than two-fold higher detection rate of women with CIN2+ histology than Pap smear cytology. *Br J Cancer.* 118(6):896–904. doi:10.1038/bjc.2017.485 PMID:29438367

Haguenoer K, Sengchanh S, Gaudy-Graffin C, Boyard J, Fontenay R, Marret H, et al. (2014). Vaginal self-sampling is a cost-effective way to increase participation in a cervical cancer screening programme: a randomised trial. *Br J Cancer.* 111(11):2187–96. doi:10.1038/bjc.2014.510 PMID:25247320

Hanske J, Meyer CP, Sammon JD, Choueiri TK, Menon M, Lipsitz SR, et al. (2016). The influence of marital status on the use of breast, cervical, and colorectal cancer screening. *Prev Med.* 89:140–5. doi:10.1016/j.ypmed.2016.05.017 PMID:27215758

Harder E, Juul KE, Jensen SM, Thomsen LT, Frederiksen K, Kjaer SK (2018a). Factors associated with non-participation in cervical cancer screening – a nationwide study of nearly half a million women in Denmark. *Prev Med.* 111:94–100. doi:10.1016/j.ypmed.2018.02.035 PMID:29501474

Harder E, Thomsen LT, Hertzum-Larsen R, Albieri V, Hessner MV, Juul KE, et al. (2018b). Determinants for participation in human papillomavirus self-sampling among nonattenders to cervical cancer screening in Denmark. *Cancer Epidemiol Biomarkers Prev.* 27(11):1342–51. doi:10.1158/1055-9965.EPI-18-0480 PMID:30108095

Hiatt RA, Pasick RJ, Stewart S, Bloom J, Davis P, Gardiner P, et al. (2008). Cancer screening for underserved women: the Breast and Cervical Cancer Intervention Study. *Cancer Epidemiol Biomarkers Prev.* 17(8):1945–9. doi:10.1158/1055-9965.EPI-08-0172 PMID:18708383

Huchko MJ, Ibrahim S, Blat C, Cohen CR, Smith JS, Hiatt RA, et al. (2018). Cervical cancer screening through human papillomavirus testing in community health campaigns versus health facilities in rural western Kenya. *Int J Gynaecol Obstet.* 141(1):63–9. doi:10.1002/ijgo.12415 PMID:29197067

IARC (2005). Cervix cancer screening. *IARC Handb Cancer Prev.* 10:1–302. Available from: https://publications.iarc.fr/380.

Idowu A, Olowookere SA, Fagbemi AT, Ogunlaja OA (2016). Determinants of cervical cancer screening uptake among women in Ilorin, North Central Nigeria: a community-based study. *J Cancer Epidemiol.* 2016:6469240. doi:10.1155/2016/6469240 PMID:26880916

Ivanus U, Jerman T, Fokter AR, Takac I, Prevodnik VK, Marcec M, et al. (2018). Randomised trial of HPV self-sampling among non-attenders in the Slovenian cervical screening programme ZORA: comparing three different screening approaches. *Radiol Oncol.* 52(4):399–412. doi:10.2478/raon-2018-0036 PMID:30216191

Iyer AL, Bundorf MK, Gyrd-Hansen D, Goldhaber-Fiebert JD, Cyr PR, Sønbø Kristiansen I (2019). How does information on the harms and benefits of cervical cancer screening alter the intention to be screened?: a randomized survey of Norwegian women. *Eur J Cancer Prev.* 28(2):87–95. doi:10.1097/CEJ.0000000000000436 PMID:29595751

Jensen H, Svanholm H, Støvring H, Bro F (2009). A primary healthcare-based intervention to improve a Danish cervical cancer screening programme: a cluster randomised controlled trial. *J Epidemiol Community Health.* 63(7):510–5. doi:10.1136/jech.2008.077636 PMID:19228681

Kangmennaang J, Onyango EO, Luginaah I, Elliott SJ (2018). The next Sub Saharan African epidemic? A case study of the determinants of cervical cancer knowledge and screening in Kenya. *Soc Sci Med.* 197:203–12. doi:10.1016/j.socscimed.2017.12.013 PMID:29253722

Kellen E, Benoy I, Vanden Broeck D, Martens P, Bogers JP, Haelens A, et al. (2018). A randomized, controlled trial of two strategies of offering the home-based HPV self-sampling test to non-participants in the Flemish

cervical cancer screening program. *Int J Cancer.* 143(4):861–8. doi:10.1002/ijc.31391 PMID:29569715

Kim K, Kim S, Gallo JJ, Nolan MT, Han HR (2017). Decision making about Pap test use among Korean immigrant women: a qualitative study. *Health Expect.* 20(4):685–95. doi:10.1111/hex.12507 PMID:27687295

Kitchener H, Gittins M, Cruickshank M, Moseley C, Fletcher S, Albrow R, et al. (2018). A cluster randomized trial of strategies to increase uptake amongst young women invited for their first cervical screen: the STRATEGIC trial. *J Med Screen.* 25(2):88–98. doi:10.1177/0969141317696518 PMID:28530513

Kobetz E, Seay J, Koru-Sengul T, Bispo JB, Trevil D, Gonzalez M, et al. (2018). A randomized trial of mailed HPV self-sampling for cervical cancer screening among ethnic minority women in South Florida. *Cancer Causes Control.* 29(9):793–801. doi:10.1007/s10552-018-1055-7 PMID:29995217

Lazcano-Ponce E, Lorincz AT, Cruz-Valdez A, Salmerón J, Uribe P, Velasco-Mondragón E, et al. (2011). Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. *Lancet.* 378(9806):1868–73. doi:10.1016/S0140-6736(11)61522-5 PMID:22051739

León-Maldonado L, Allen-Leigh B, Lazcano-Ponce E (2014). Counseling for HPV detection when used to screen for cervical cancer: a qualitative study on the needs of women from Michoacán, Mexico. [in Spanish] *Salud Publica Mex.* 56(5):519–27. doi:10.21149/spm.v56i5.7377 PMID:25604297

León-Maldonado L, Wentzell E, Brown B, Allen-Leigh B, Torres-Ibarra L, Salmerón J, et al. (2016). Perceptions and experiences of human papillomavirus (HPV) infection and testing among low-income Mexican women. *PLoS One.* 11(5):e0153367. doi:10.1371/journal.pone.0153367 PMID:27149525

Liebermann EJ, VanDevanter N, Hammer MJ, Fu MR (2018). Social and cultural barriers to women's participation in Pap smear screening programs in low- and middle-income Latin American and Caribbean countries: an integrative review. *J Transcult Nurs.* 29(6):591–602. doi:10.1177/1043659618755424 PMID:29366369

Lim JN, Ojo AA (2017). Barriers to utilisation of cervical cancer screening in Sub Sahara Africa: a systematic review. *Eur J Cancer Care (Engl).* 26(1):e12444. doi:10.1111/ecc.12444 PMID:26853214

Magee CG, Hult JR, Turalba R, McMillan S (2005). Preventive care for women in prison: a qualitative community health assessment of the Papanicolaou test and follow-up treatment at a California state women's prison. *Am J Public Health.* 95(10):1712–7. doi:10.2105/AJPH.2005.063677 PMID:16186450

Mandal R, Basu P (2018). Cancer screening and early diagnosis in low and middle income countries: current situation and future perspectives. *Bundesgesundheitsblatt*

Gesundheitsforschung Gesundheitsschutz. 61(12):1505–12. doi:10.1007/s00103-018-2833-9 PMID:30353287

Marlow L, McBride E, Varnes L, Waller J (2019). Barriers to cervical screening among older women from hard-to-reach groups: a qualitative study in England. *BMC Womens Health*. 19(1):38. doi:10.1186/s12905-019-0736-z PMID:30808349

Marlow LA, Waller J (2014). Communicating the changes to cervical cancer screening in England: the choice to have an HPV test. *Womens Health (Lond)*. 10(3):221–3. doi:10.2217/WHE.14.12 PMID:24956287

Marques P, Nunes M, Antunes MDL, Heleno B, Dias S (2020). Factors associated with cervical cancer screening participation among migrant women in Europe: a scoping review. *Int J Equity Health*. 19(1):160. doi:10.1186/s12939-020-01275-4 PMID:32917224

McCaffery KJ, Irwig L, Chan SF, Macaskill P, Barratt A, Lewicka M, et al. (2008). HPV testing versus repeat Pap testing for the management of a minor abnormal Pap smear: evaluation of a decision aid to support informed choice. *Patient Educ Couns*. 73(3):473–9, 481. doi:10.1016/j.pec.2008.07.021 PMID:18757164

McCaffery KJ, Turner R, Macaskill P, Walter SD, Chan SF, Irwig L (2011). Determining the impact of informed choice: separating treatment effects from the effects of choice and selection in randomized trials. *Med Decis Making*. 31(2):229–36. doi:10.1177/0272989X10379919 PMID:21041538

Mishra SI, Luce PH, Baquet CR (2009). Increasing Pap smear utilization among Samoan women: results from a community based participatory randomized trial. *J Health Care Poor Underserved*. 20(2 Suppl):85–101. doi:10.1353/hpu.0.0160 PMID:19711495

Mock J, McPhee SJ, Nguyen T, Wong C, Doan H, Lai KQ, et al. (2007). Effective lay health worker outreach and media-based education for promoting cervical cancer screening among Vietnamese American women. *Am J Public Health*. 97(9):1693–700. doi:10.2105/AJPH.2006.086470 PMID:17329652

Modibbo F, Iregbu KC, Okuma J, Leeman A, Kasius A, de Koning M, et al. (2017). Randomized trial evaluating self-sampling for HPV DNA based tests for cervical cancer screening in Nigeria. *Infect Agent Cancer*. 12(1):11. doi:10.1186/s13027-017-0123-z PMID:28184239

Morema EN, Atieli HE, Onyango RO, Omondi JH, Ouma C (2014). Determinants of cervical screening services uptake among 18–49 year old women seeking services at the Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu, Kenya. *BMC Health Serv Res*. 14(1):335. doi:10.1186/1472-6963-14-335 PMID:25100298

Morrell S, Taylor R, Zeckendorf S, Niciak A, Wain G, Ross J (2005). How much does a reminder letter increase cervical screening among under-screened women in NSW? *Aust N Z J Public Health*. 29(1):78–84. doi:10.1111/j.1467-842X.2005.tb00753.x PMID:15782877

Moses E, Pedersen HN, Mitchell SM, Sekikubo M, Mwesigwa D, Singer J, et al. (2015). Uptake of community-based, self-collected HPV testing vs. visual inspection with acetic acid for cervical cancer screening in Kampala, Uganda: preliminary results of a randomised controlled trial. *Trop Med Int Health*. 20(10):1355–67. doi:10.1111/tmi.12549 PMID:26031572

Mullins RM (2009). Can older women be motivated to attend for their final Papanicolaou tests? The use of targeted and general personalised reminder letters. *Cancer Epidemiol*. 33(3–4):306–8. doi:10.1016/j.canep.2009.08.007 PMID:19748846

Musa J, Achenbach CJ, O'Dwyer LC, Evans CT, McHugh M, Hou L, et al. (2017). Effect of cervical cancer education and provider recommendation for screening on screening rates: a systematic review and meta-analysis. [published correction appears in PLoS One. 2017 Dec 29;12 (12):e0190661]. *PLoS One*. 12(9):e0183924. doi:10.1371/journal.pone.0183924 PMID:28873092

Nuche-Berenguer B, Sakellariou D (2019). Socioeconomic determinants of cancer screening utilisation in Latin America: a systematic review. *PLoS One*. 14(11):e0225667. doi:10.1371/journal.pone.0225667 PMID:31765426

Nuño T, Martinez ME, Harris R, García F (2011). A *Promotora*-administered group education intervention to promote breast and cervical cancer screening in a rural community along the U.S.–Mexico border: a randomized controlled trial. *Cancer Causes Control*. 22(3):367–74. doi:10.1007/s10552-010-9705-4 PMID:21184267

Nwobodo H, Ba-Break M (2015). Analysis of the determinants of low cervical cancer screening uptake among Nigerian women. *J Public Health Africa*. 6(2):484. doi:10.4081/jphia.2015.484 PMID:28299143

O'Brien MJ, Halbert CH, Bixby R, Pimentel S, Shea JA (2010). Community health worker intervention to decrease cervical cancer disparities in Hispanic women. *J Gen Intern Med*. 25(11):1186–92. doi:10.1007/s11606-010-1434-6 PMID:20607434

Osingada CP, Ninsiima G, Chalo RN, Muliira JK, Ngabirano T (2015). Determinants of uptake of cervical cancer screening services at a no-cost reproductive health clinic managed by nurse-midwives. *Cancer Nurs*. 38(3):177–84. doi:10.1097/NCC.0000000000000156 PMID:24831038

Palència L, Espelt A, Rodríguez-Sanz M, Puigpinós R, Pons-Vigués M, Pasarín MI, et al. (2010). Socioeconomic inequalities in breast and cervical cancer screening practices in Europe: influence of the type of screening program. *Int J Epidemiol*. 39(3):757–65. doi:10.1093/ije/dyq003 PMID:20176587

Paskett ED, McLaughlin JM, Lehman AM, Katz ML, Tatum CM, Oliveri JM (2011). Evaluating the efficacy of lay health advisors for increasing risk-appropriate Pap test screening: a randomized controlled trial among Ohio Appalachian women. *Cancer Epidemiol Biomarkers Prev*. 20(5):835–43. doi:10.1158/1055-9965. EPI-10-0880 PMID:21430302

Peeters E, Cornet K, Devroey D, Arbyn M (2020). Efficacy of strategies to increase participation in cervical cancer screening: GPs offering self-sampling kits for HPV testing versus recommendations to have a Pap smear taken – a randomised controlled trial. *Papillomavirus Res*. 9:100194. doi:10.1016/j.pvr.2020.100194 PMID:32179181

Piana L, Leandri F-X, Le Retraite L, Heid P, Tamalet C, Sancho-Garnier H (2011). HPV-Hr detection by home self sampling in women not compliant with Pap test for cervical cancer screening. Results of a pilot programme in Bouches-du-Rhône. [in French] *Bull Cancer*. 98(7):723–31. doi:10.1684/bdc.2011.1388 PMID:21700548

Racey CS, Gesink DC, Burchell AN, Trivers S, Wong T, Rebbapragada A (2016). Randomized intervention of self-collected sampling for human papillomavirus testing in under-screened rural women: uptake of screening and acceptability. *J Womens Health (Larchmt)*. 25(5):489–97. doi:10.1089/jwh.2015.5348 PMID:26598955

Radde K, Gottschalk A, Bussas U, Schülein S, Schriefer D, Seifert U, et al. (2016). Invitation to cervical cancer screening does increase participation in Germany: results from the MARZY study. *Int J Cancer*. 139(5):1018–30. doi:10.1002/ijc.30146 PMID:27083776

Rahman R, Clark MD, Collins Z, Traore F, Dioukhane EM, Thiam H, et al. (2019). Cervical cancer screening decentralized policy adaptation: an African rural-context-specific systematic literature review. *Glob Health Action*. 12(1):1587894. doi:10.1080/16549716.2019.1587894 PMID:30938248

Ramjan L, Cotton A, Algoso M, Peters K (2016). Barriers to breast and cervical cancer screening for women with physical disability: a review. *Women Health*. 56(2):141–56. doi:10.1080/03630242.2015.1086463 PMID:26325597

Rashid RMA, Mohamed M, Hamid ZA, Dahlui M (2013). Is the phone call the most effective method for recall in cervical cancer screening? – results from a randomised control trial. *Asian Pac J Cancer Prev*. 14(10):5901–4. doi:10.7314/APJCP.2013.14.10.5901 PMID:24289597

Restivo V, Costantino C, Marras A, Napoli G, Scelfo S, Scuderi T, et al. (2018). Pap testing in a high-income country with suboptimal compliance levels: a survey on acceptance factors among Sicilian women. *Int J Environ Res Public Health*. 15(9):1804. doi:10.3390/ijerph15091804 PMID:30131461

Ryan M, Waller J, Marlow LA (2019). Could changing invitation and booking processes help women translate their cervical screening intentions into action? A population-based survey of women's preferences in Great Britain. *BMJ Open*. 9(7):e028134. doi:10.1136/bmjopen-2018-028134 PMID:31300499

Sabatino SA, Lawrence B, Elder R, Mercer SL, Wilson KM, DeVinney B, et al.; Community Preventive Services Task Force (2012). Effectiveness of interventions to increase screening for breast, cervical, and colorectal cancers: nine updated systematic reviews for the guide to community preventive services. *Am J Prev Med*. 43(1):97–118. doi:10.1016/j.amepre.2012.04.009 PMID:22704754

Sancho-Garnier H, Tamalet C, Halfon P, Leandri FX, Le Retraite L, Djoufelkit K, et al. (2013). HPV self-sampling or the Pap-smear: a randomized study among cervical screening nonattenders from lower socioeconomic groups in France. *Int J Cancer*. 133(11):2681–7. doi:10.1002/ijc.28283 PMID:23712523

Schoenberg N, Baltisberger J, Bardach S, Dignan M (2010). Perspectives on Pap test follow-up care among rural Appalachian women. *Women Health*. 50(6):580–97. doi:10.1080/03630242.2010.516702 PMID:20981638

Serman F, Favre J, Deken V, Guittet L, Collins C, Rochoy M, et al. (2020). The association between cervical cancer screening participation and the deprivation index of the location of the family doctor's office. *PLoS One*. 15(5):e0232814. doi:10.1371/journal.pone.0232814 PMID:32413044

Sewali B, Okuyemi KS, Askhir A, Belinson J, Vogel RI, Joseph A, et al. (2015). Cervical cancer screening with clinic-based Pap test versus home HPV test among Somali immigrant women in Minnesota: a pilot randomized controlled trial. *Cancer Med*. 4(4):620–31. doi:10.1002/cam4.429 PMID:25653188

Smith RA, Hernandez R, Catona D (2014). Investigating initial disclosures and reactions to unexpected, positive HPV diagnosis. *West J Commun*. 78(4):426–40. doi:10.1080/10570314.2013.786120 PMID:25642121

Solar O, Irwin A (2010). A conceptual framework for action on the social determinants of health. Social Determinants of Health Discussion Paper 2 (policy and practice). Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/sdhconference/resources/ConceptualframeworkforactiononSDH_eng.pdf.

Soneji S, Fukui N (2013). Socioeconomic determinants of cervical cancer screening in Latin America. *Rev Panam Salud Publica*. 33(3):174–82. doi:10.1590/S1020-49892013000300003 PMID:23698136

Sultana F, English DR, Simpson JA, Drennan KT, Mullins R, Brotherton JML, et al. (2016). Home-based HPV self-sampling improves participation by never-screened and under-screened women: results from a

large randomized trial (iPap) in Australia. *Int J Cancer*. 139(2):281–90. doi:10.1002/ijc.30031 PMID:26850941

Suurmond J, Seeleman C (2006). Shared decision-making in an intercultural context. Barriers in the interaction between physicians and immigrant patients. *Patient Educ Couns*. 60(2):253–9. doi:10.1016/j.pec.2005.01.012 PMID:16442467

Szarewski A, Cadman L, Mesher D, Austin J, Ashdown-Barr L, Edwards R, et al. (2011). HPV self-sampling as an alternative strategy in non-attenders for cervical screening – a randomised controlled trial. *Br J Cancer*. 104(6):915–20. doi:10.1038/bjc.2011.48 PMID:21343937

Taylor VM, Jackson JC, Yasui Y, Nguyen TT, Woodall E, Acorda E, et al. (2010). Evaluation of a cervical cancer control intervention using lay health workers for Vietnamese American women. *Am J Public Health*. 100(10):1924–9. doi:10.2105/AJPH.2009.190348 PMID:20724673

Thompson B, Carosso EA, Jhingan E, Wang L, Holte SE, Byrd TL, et al. (2017). Results of a randomized controlled trial to increase cervical cancer screening among rural Latinas. *Cancer*. 123(4):666–74. doi:10.1002/cncr.30399 PMID:27787893

Tracy JK, Schluterman NH, Greenberg DR (2013). Understanding cervical cancer screening among lesbians: a national survey. *BMC Public Health*. 13(1):442. doi:10.1186/1471-2458-13-442 PMID:23642184

Tranberg M, Bech BH, Blaakær J, Jensen JS, Svanholm H, Andersen B (2018). Preventing cervical cancer using HPV self-sampling: direct mailing of test-kits increases screening participation more than timely opt-in procedures – a randomized controlled trial. *BMC Cancer*. 18(1):273. doi:10.1186/s12885-018-4165-4 PMID:29523108

Virtanen A, Nieminen P, Luostarinen T, Anttila A (2011). Self-sample HPV tests as an intervention for nonattendees of cervical cancer screening in Finland: a randomized trial. *Cancer Epidemiol Biomarkers Prev*. 20(9):1960–9. doi:10.1158/1055-9965.EPI-11-0307 PMID:21752985

Visanuyothin S, Chompikul J, Mongkolchati A (2015). Determinants of cervical cancer screening adherence in urban areas of Nakhon Ratchasima Province, Thailand. *J Infect Public Health*. 8(6):543–52. doi:10.1016/j.jiph.2015.04.018 PMID:25975994

Viviano M, Catarino R, Jeannot E, Boulvain M, Malinverno MU, Vassilakos P, et al. (2017). Self-sampling to improve cervical cancer screening coverage in Switzerland: a randomised controlled trial. *Br J Cancer*. 116(11):1382–8. doi:10.1038/bjc.2017.111 PMID:28427086

Weyers S, Garland SM, Cruickshank M, Kyrgiou M, Arbyn M (2021). Cervical cancer prevention in transgender men: a review. *BJOG*. 128(5):822–6. doi:10.1111/1471-0528.16503 PMID:32931650

WHO (2007). Unequal, unfair, ineffective and inefficient. Gender inequity in health: why it exists and how we can change it. Available from: https://www.who.int/social_determinants/resources/csdh_media/wgekn_final_report_07.pdf?ua=1.

WHO (2008). Health systems financing. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/healthinfo/statistics/toolkit_hss/EN_PDF_Toolkit_HSS_Financing.pdf.

WHO (2013). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva, Switzerland: World Health Organization. Available from: https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/.

Wikström I, Lindell M, Sanner K, Wilander E (2011). Self-sampling and HPV testing or ordinary Pap-smear in women not regularly attending screening: a randomised study. *Br J Cancer*. 105(3):337–9. doi:10.1038/bjc.2011.236 PMID:21730977

Williams-Brennan L, Gastaldo D, Cole DC, Paszat L (2012). Social determinants of health associated with cervical cancer screening among women living in developing countries: a scoping review. *Arch Gynecol Obstet*. 286(6):1487–505. doi:10.1007/s00404-012-2575-0 PMID:23011733

Winer RL, Lin J, Tiro JA, Miglioretti DL, Beatty T, Gao H, et al. (2019). Effect of mailed human papillomavirus test kits vs usual care reminders on cervical cancer screening uptake, precancer detection, and treatment: a randomized clinical trial. *JAMA Netw Open*. 2(11):e1914729. doi:10.1001/jamanetworkopen.2019.14729 PMID:31693128

Yabroff KR, Reeder-Hayes K, Zhao J, Halpern MT, Lopez AM, Bernal-Mizrachi L, et al. (2020). Health insurance coverage disruptions and cancer care and outcomes: systematic review of published research. *J Natl Cancer Inst*. 112(7):671–87. doi:10.1093/jnci/djaa048 PMID:32337585

Yeh PT, Kennedy CE, de Vuyst H, Narasimhan M (2019). Self-sampling for human papillomavirus (HPV) testing: a systematic review and meta-analysis. *BMJ Glob Health*. 4(3):e001351. doi:10.1136/bmjgh-2018-001351 PMID:31179035

Zehbe I, Jackson R, Wood B, Weaver B, Escott N, Severini A, et al. (2016). Community-randomised controlled trial embedded in the Anishinaabek Cervical Cancer Screening Study: human papillomavirus self-sampling versus Papanicolaou cytology. *BMJ Open*. 6(10):e011754. doi:10.1136/bmjopen-2016-011754 PMID:27855089

4. PREVENTIVE AND ADVERSE EFFECTS OF CERVICAL CANCER SCREENING

4.1 Methodological issues

4.1.1 Considerations about beneficial effects of cervical screening

(a) General principles

This section considers the benefits of cervical screening, the accuracy of methods used for cervical screening and management, and the types of studies and data used to evaluate cervical screening and the related metrics to evaluate the benefits of screening.

The main goal of cervical screening is the prevention of invasive cervical cancer by the detection and treatment of intraepithelial precancer (see Section 1.2). This needs to be distinguished from downstaging, which is the early detection and treatment of already invasive cancer to improve the chance of a cure; downstaging is the main goal of screening for cancer types that lack well-defined, treatable precancerous precursors. Successful detection and treatment of precancers should lead to a reduction in cervical cancer incidence and mortality. Successful stage shift should lead to a reduction in cervical cancer mortality.

The theoretical maximum possible benefit of cervical screening in a population is the complete secondary prevention of invasive cancer by detecting and treating all cervical precancers that would progress to invasive cancer. The cumulative lifetime incidence of cervical cancer ranges from 1% to 5% of all women; for the other women, cervical cancer screening does not bring any benefits on a personal basis because they will never have the disease in any case, and thus it is essential to pay attention to its possible harms.

The use of cervical cancer screening with Pap cytology became widespread in many high-income countries during the late 1960s and the 1970s, before randomized trials became the standard for evaluating the efficacy of preventive interventions. Because of this, the initial evidence on the efficacy of cervical cancer screening was derived from ecological or surveillance data, cohort studies, and case–control studies (for details, see Section 4.3.2).

(b) Diagnostic accuracy

For a screening test to be accurate, it must, as a primary requirement, yield approximately the same result when repeated in the same and different test settings. Some tests are inherently subjective and often yield non-reproducible results in the case of minor cytological or minor visual abnormalities. Such tests are bound to be inaccurate.

Whatever type of cervical test is being evaluated, the same statistical analyses are applied to assess accuracy. Continuous or ordinal measurements (e.g. the viral load measured by a human papillomavirus [HPV] test or the

grades of cytological abnormality) are typically combined into a few categories before analysis (e.g. positive/negative or abnormal/normal). The accuracy of a screening test is measured as a trade-off between sensitivity and specificity, which are the well-known measures of test performance given outcome category (sensitivity is test positivity among precancers; specificity is test negativity given the absence of precancer or cancer). Sensitivity and specificity can be estimated with any major study design, including the common case–control study. An important derivative statistic that is based on sensitivity and specificity is the area under the curve (AUC) of a receiver operating characteristic (ROC) curve, which evaluates sensitivity and specificity over a wide range of cut-off values.

For the evaluation of screening tests, we distinguish between analytical accuracy and clinical accuracy. Analytical accuracy relates to the target of detection (e.g. HPV DNA), whereas clinical accuracy relates to the detection of cervical precancer. Achieving maximal analytical sensitivity is not the primary goal of cervical screening tests. HPV infection and its associated microscopic and visual abnormalities are common and are typically benign. The prevalence of HPV varies greatly by age and population and can be very high in some settings. A positive HPV test result (or low-grade squamous intraepithelial lesion [LSIL] cytology or visual impression of acetowhitening), which accurately detects infection with a carcinogenic HPV type, is, in the context of risk of precancer, a false-positive result, because most infections resolve or become undetectable without intervention. Unlike the situation for other infectious agents, considering all positive analytical test results to indicate a positive cervical screening result leads to poor specificity and low positive predictive value (PPV) in screening for cervical precancer. The challenge of cervical screening is to choose tests and thresholds that maximize accuracy for

diagnosis of precancer as distinct from benign HPV effects.

Evaluating the accuracy of screening tests typically involves testing followed by the systematic application of the reference standard test, traditionally colposcopy-directed biopsy of all acetowhite lesions (Wentzensen et al., 2015), to all women enrolled in a relevant study population. All tests, including the reference standard, should be performed independently and within a very short time period. The principles and reporting standards for diagnostic accuracy studies are summarized by the Standards for Reporting of Diagnostic Accuracy Studies (STARD) criteria (Bossuyt et al., 2015). The quality of diagnostic accuracy studies included in a meta-analysis can be assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist (Clarke et al., 2020).

It is not feasible or economically viable to apply the reference standard test to large populations of women attending cervical cancer screening; this would also be unethical, because it would result in a large number of women with a very low likelihood of having precancer undergoing colposcopy and biopsy. Clinical practice in cervical cancer screening usually involves a screening test, sometimes followed by triage; triage-positive or screen-positive women are referred for colposcopy and biopsy. Therefore, real-life screening data may suffer from partial and differential verification bias when absolute accuracy is estimated. When the screening test (e.g. visual inspection with acetic acid [VIA] or visual inspection with Lugol's iodine [VILI]) and the reference standard test (e.g. colposcopy) are subjective and correlated, this can lead to severely biased estimates (Arbyn et al., 2008a), unless intrinsic correlation is accounted for statistically (Leeflang & Reitsma, 2018). However, the risk of a cancer or even a precancer in women with a negative HPV test result is so low that it is not necessary to refer a fraction of HPV-negative women for further verification when a well-validated HPV

DNA test is used for primary screening. In fact, adjustment for verification bias in HPV-negative women can lead to substantial distortions in the estimates of test accuracy (Castle et al., 2020). Verification bias is usually a minor issue when relative accuracy (comparing one test directly with another) is assessed.

The design and evaluation of screening approaches depend on precise definition of the screening target. Precancer is the causal surrogate for cancer risk in this context; if defined formally, a reduction in precancer should translate into the same proportional reduction in cancer. However, there are no markers that accurately identify the lesions that would progress to cancer. Cervical cancer screening studies are usually based on cervical intraepithelial neoplasia grade 2 or worse (CIN2+) or CIN grade 3 or worse (CIN3+) as end-points. CIN3+ is a more reliable outcome, because this diagnosis is more reproducible and is more strongly associated with progression to cancer. If precancer is defined too broadly (e.g. including a subset of CIN2 caused by HPV types that are almost never found in cancer), tests evaluated against this inflated standard will have distorted evaluations. For example, an HPV test that correctly targets only the truly carcinogenic types would be incorrectly criticized for lack of sensitivity rather than being recognized for increased specificity. Although it is preferable to use CIN3/adenocarcinoma in situ (AIS) as the end-point in screening evaluations, treatment of CIN2 can lead to underestimation of risk of CIN3 because some of the treated CIN2 would progress to CIN3. This does not affect CIN3+ end-points in cross-sectional studies of previously unscreened individuals.

(c)   Randomized screening trials

To study the health effects of a new screening technology in real-world screening settings, randomized screening trials have been conducted in several countries. Screening trials are pragmatic trials (Schwartz & Lellouch, 1967, 2009) embedded in routine screening with few additional inclusion criteria, and with realistic triage and management of surveillance. The intervention effect measured in such pragmatic trials will be close to the effect observed when implementing the new technology in the real world, and its interpretation will not be limited to the study trial.

The ultimate goal of cancer screening is the reduction of cancer mortality, but the effect on cancer mortality is very difficult to measure in countries with screening in place, and it has only been assessed in a previously unscreened population (Sankaranarayanan et al., 2009). The same limitations exist for the end-point cancer, which has only been studied in a pooled analysis of European screening trials (Ronco et al., 2014). Other screening trials have CIN3+ or CIN2+ as the primary end-point.

Randomized screening trials aim to directly estimate the effect of switching technology on the detection of CIN3+ and CIN2+ over one or two screening rounds. Results in the first round can also be studied by a prospective study, where the new and conventional technologies are used in parallel and women are managed on the basis of the results of all tests. However, the randomized trial and the combined testing design may give different results when the results from the new and conventional technologies are dependent for reasons unrelated to the development of cervical cancer. This is illustrated by two examples. The first example is a study in which primary HPV testing with cytological testing on HPV-positive samples is compared with cytology alone. The performance of cytology may be influenced by knowledge of the HPV status. A valid estimate of the effect of HPV testing on CIN3+ detection can be obtained through a randomized trial in which cytotechnicians in the intervention group are informed about the HPV status of the samples (Leinonen et al., 2012). The second example is a study in which liquid-based cytology is compared with conventional cytology. With the combined

testing design, the sampling procedure may place the second test at a disadvantage because cells for diagnosis have been removed by the first sample. This potential sampling effect can be avoided by randomizing women to one of the two test typesl (Ronco et al., 2007).

In most cervical cancer screening trials, participants are followed up for more than one screening round. Because the purpose of screening is to prevent cancer through the detection of precancer, the main aim of trials with CIN2+ or CIN3+ as end-points is to show that the new technology increases the lead-time gain from screening. This can be done by showing that increased detection of CIN2+ and CIN3+ in the first round of screening is followed by decreased detection in the second round.

Randomized screening trials vary in how they define the second round. Some trials categorize all CIN2+ and CIN3+ detected beyond a certain time point as in the second round (Rijkaart et al., 2012; Ogilvie et al., 2018). The strength of this approach is that a decreased detection of CIN2+ or CIN3+ in the second round can be explained by earlier detection, because randomization ensures that the risks of precancer at baseline are equal in the two study arms. The approach works well when the screening interval is long enough to ensure that all women in the comparison group have completed the first round. Otherwise, it may be better to select women for whom completion of the first round can be confirmed. To minimize the chance that the impact on lead-time gain is distorted by baseline differences between subgroups in the risk of precancer, the second round should include not only follow-up of women with a negative screening test result at baseline but also follow-up of screen-positive women with a negative test result at short-term repeat testing (Chan et al., 2020) and follow-up of women who underwent surveillance after colposcopy (Ronco et al., 2010).

Randomized screening trials also vary with respect to the choice of technology in the second round. Some trials use only the conventional technology in both arms (Naucler et al., 2007; Ronco et al., 2010), whereas others use the new technology in both arms (Rijkaart et al., 2012; Ogilvie et al., 2018) or retain separate screening strategies in the two arms (Kitchener et al., 2009). This may influence the trial results. For example, some of the precancers may remain undetected in women who are offered conventional technology in the first and second round, in particular when the difference in lead-time gain between the two technologies is large.

(d) Observational studies

Observational data play an important role in evaluating and improving cervical cancer screening programmes. Observational data range from ecological studies involving cancer registries to specific cohort studies that directly compare screening tests and strategies.

Cytology screening was introduced without evidence from randomized trials. Large decreases in the incidence of cervical cancer after the rapid implementation of cervical screening in some populations provided evidence of the effectiveness of cervical screening even from study designs that are typically not considered to be sufficient to prove causal associations between an intervention and a health effect. For example, large reductions in the incidence of cervical cancer were seen in Finland, Slovenia, and the United Kingdom after the implementation of national call–recall organized programmes (Quinn et al., 1999; Anttila, 2007; ZORA, 2018). Furthermore, the implementation of organized programmes in European countries, including Denmark, Finland, Italy, the Netherlands, Sweden, and the United Kingdom (Anttila et al., 2009), and integrated health systems in the USA, including Kaiser Permanente Northern California (Castle et al., 2018), as well as experiences with opportunistic screening in the Republic of Korea

(Odongua et al., 2007) and the USA (Landy et al., 2020), have led to the development of an infrastructure for the systematic collection of routine data on screening tests, results, and outcomes from screening and pathology registries. Many screening programmes continue to provide insights into the effectiveness of different screening protocols (Rebolj et al., 2008; Briët et al., 2010) and new technologies (Akamatsu et al., 2012; Rebolj et al., 2015; Rozemeijer et al., 2017; Forslund et al., 2019; Zorzi et al., 2020).

One of the strengths of these population-based studies is that, given the implementation of a programme that targets an entire population, it is possible to evaluate intention-to-treat approaches in cohort studies (e.g. Ronco et al., 2005), which reduces bias related to indication. When historical or geographical controls are used, the comparability of populations, even in the absence of indication bias, is a concern, particularly when two screened populations are compared to evaluate different protocols or technologies. In fact, two main determinants of cervical disease outcomes – the screening history (Maggino et al., 2016; Castle et al., 2019) and the prevalence of HPV (Bray et al., 2005; Sander et al., 2014) – can change rapidly over time and vary by geographical region.

Retrospective cohort studies examining sensitivity and efficacy against cancer have been used to compare screening tests; however, this study design has important methodological issues, which can lead to severely biased estimates when they are not properly accounted for. For example, studies that use a cancer diagnosis or the detection of a high-grade precursor lesion as a starting point and retrospectively select on previous screening results may be biased in favour of cytology when the management is differential between cytology and other tests and the screening history is limited (Blatt et al., 2015; Castle, 2015; Giorgi Rossi et al., 2016; Kaufman et al., 2020; Schiffman & Wentzensen, 2021). The choice of end-point is also meaningful in

retrospective studies examining the performance of screening tests, and relates to the timing of previous testing. Most screening tests performed within a short time of cancer diagnosis are part of the clinical workup (Andrae et al., 2008; Castanon et al., 2013) or represent detection of an advanced, symptomatic cancer. This study design cannot capture the screening performance of these tests as an instrument to prevent cancer by detecting precancer (Ronco & Franceschi, 2018).

Well-designed observational studies have become important pillars of regulatory evaluations of cervical screening tests. For example, recent United States Food and Drug Administration (FDA) approvals of HPV tests for primary screening, either alone or in combination with cytology, were based not on randomized trials but on prospective cohort studies in which all comparator tests were conducted in the entire population and positive results from any test led to referral for colposcopy (FDA, 2019). These studies enable the efficient comparison of disease detection for different assays in the first screening round, but because the management is not differential for different test results, they do not enable the evaluation of disease outcomes by test result in subsequent screening rounds.

(e) Risk-based screening and management

Test sensitivity and specificity do not directly inform health decisions, which require knowledge of risk (i.e. the measures of outcome based on test result). Risk is measured over a defined time period (cross-sectional or, ideally, prospective). When population data are available, optimally cohort data from an observational study or trial, health decisions about screening can be made by answering practical questions about absolute risk: What is the (pre-test) risk of developing this cancer? (This informs whether screening is worth doing.) What is the risk of developing this cancer if the test result is positive, and what should be done next? How reassuring is a negative

test result, and when should a participant with a negative test result come back for another screen?

An accurate screening test will divide the population pre-test risk (i.e. the population prevalence of precancer) into substantially higher risk (PPV defined as a function of time from screening) when a test result is positive, or lower risk (1 – negative predictive value [NPV]) when a test result is negative. Risk stratification alone (i.e. the difference in post-test risk between those with a positive test result and those with a negative test result) is not meaningful without the context of clinical action thresholds. Meaningful risk stratification implies that the post-test risk for at least one of the groups (those with a positive test result or those with a negative test result) leads to different clinical management.

No single available cervical screening test has both very high PPV and very high NPV; therefore, a second, complementary triage test is generally used, which, in combination with the first test, provides a finer and more individually accurate level of risk discrimination. When the primary screening test is sensitive (e.g. in HPV testing), it is often reasonable to use the second test only to confirm the positive result from the first test, and to save the resources that would be required to co-test everyone. The combined results of screening and triage tests are grouped into categories, and the sensitivity/specificity or predictive values/risks of the combined strategy are assessed similarly as for a single test.

The same approach applies to screening, triage, post-colposcopy management, and post-treatment management. A risk-based approach may enable practice to be unified independent of the underlying tests. The 2019 update of the consensus guidelines for management of cervical cancer screening abnormalities (Perkins et al., 2020) adopted this principle as the foundation of the clinical guidelines. It is important to evaluate whether absolute risk estimates are portable between different populations. Even if the risk estimates apply across different populations, the

decision thresholds may be adapted to clinical and societal preferences in different settings.

4.1.2 Considerations about harms of cervical screening

All cancer screening programmes involve potential harms, which individuals must balance against the potential benefits in deciding whether to participate in screening. Potential physical and psychological harms are considered in detail for each screening intervention or diagnostic step reviewed in this *Handbook*. Social and economic harms are generally not considered. Physical harms (e.g. pain, bleeding, and discharge) include those experienced because of the application of the initial screening test, as a consequence of follow-up, confirmatory, or diagnostic tests for women who receive a positive test result, or during or after treatment for screen-detected lesions. Psychological harms (e.g. anxiety and distress) may occur before, during, or after screening and may relate to the screening experience itself or to the receipt of the results and the perceived implications for the individual who has undergone a screening test, diagnostic test, or treatment procedures. Some harms, for example those that occur because of a false-positive test result, come about as a result of test characteristics or the screening system itself, and may not be observable directly by women or their clinicians. These harms may have effects at the population level; for example, false-positive screening test results may lead to unnecessary examinations and treatments, which, consequently, cause harm to women and waste medical resources. When policy-makers decide whether to implement a population-based screening programme, they must explicitly weigh the balance of potential benefits against potential harms at the population level (see Section 2.3). Fig. 4.1 presents a schematic overview of the potential harms associated with the cervical screening pathway.

Fig. 4.1 Potential harms associated with the cervical screening pathway
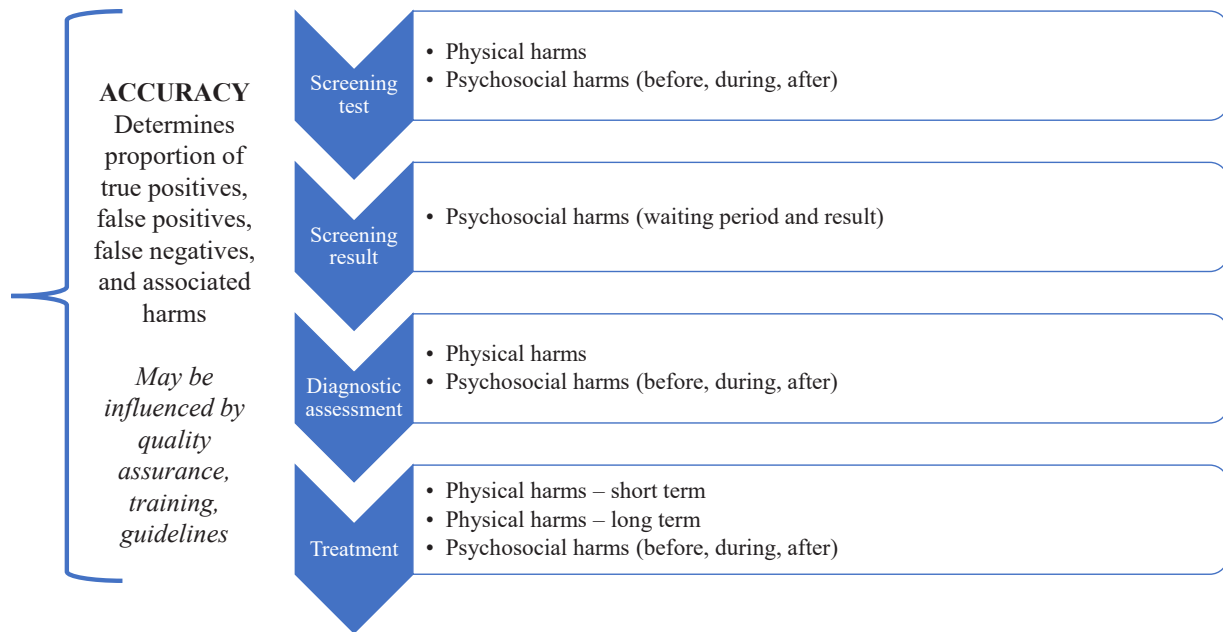
Created by the Working Group.

Harms pertaining to any screening technique are presented in this section. Evidence relating to potential harms specific to a technique, including their nature and rates of occurrence as observed during screening, is provided by technique in the relevant sections of this *Handbook* for screening by visual inspection (see Section 4.2.3), cytology (see Section 4.3.5), HPV testing (see Section 4.4.8), colposcopy (see Section 4.5), and treatment (see Section 1.2.5).

Ideally, a screening test to be used in a population will have a high NPV, which enables most women at risk of cervical cancer to be identified and the women with a negative test result to be correctly reassured that they are at low risk until the next screening test is due. The number of women potentially harmed can be measured as 1/PPV, which is the number of positive screening test results needed to confirm one precancer. Because of the natural history of HPV infection and disease (see Sections 1.2.1 and 1.2.2),

the choice of screening interval, as well as the specificity of the test itself, will influence the rate of false-positive test results. Given the transient nature of most HPV infections, screening very frequently, either for HPV infection or for the cellular or visual changes associated with it, will be more likely to identify acute infection or disease with no potential for malignancy, thus increasing the proportion and number of false-positive test results and the potential harms.

Some of the concepts relevant to the monitoring of harms in cervical cancer screening programmes are discussed here.

(a)   Overscreening

Cervical cancer screening that is carried out more frequently than is recommended in the current guidelines or that is used in a wider target age range or after hysterectomy can be called overscreening. The results from a decision analysis suggested that a short screening

193

Table 4.1 Harms associated with cervical cancer screening and management of screen-positive women in the USA and the Netherlands in 2007[a]

Event	Events per 1000 women		USA:Netherlands ratio
	USA	Netherlands	
Pap test			
Number	394	164	2.4
Symptoms[b] for at least 2–7 days	51	21	2.4
Abnormal test results			
Number	25	9	2.8
Anxiety for at least 12 weeks	9	3	3.0
Punch biopsy			
Number	16.9	4.3	3.9
Light[c] symptoms	19	5	3.8
Moderate or strong[c] symptoms	11	3	3.7
Treatment			
Number	3.0	1.8	1.7
Light[c] symptoms	2.4	1.4	1.7
Moderate or strong[c] symptoms	3.8	2.3	1.7

[a] Data were standardized to the female population of the USA aged 21–65 years in 2007.

[b] Lower abdominal pain, urinary discomfort, feeling sick, feeling dizzy, and/or painful sexual activity.

[c] Light refers to very light or light pain, bleeding, or discharge; moderate or strong refers to moderate, severe, or very severe pain, bleeding, or discharge.

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interval and the use of HPV screening in women younger than 30 years will lead to an increase in the number of unnecessary colposcopies (Kim et al., 2018). Based on a systematic review, the main types of overscreening are screening that is too frequent (more frequent than the guideline recommendation), screening after hysterectomy, screening started before the recommended age, and screening after the recommended age at which screening should be stopped (Alber et al., 2018; Kim et al., 2018). A study in France reviewed outcomes for 63 821 women aged 25–65 years screened for up to 9 years, 37% of whom underwent cervical cancer screening at the recommended interval (every 3 years) and 63% more frequently. Overscreened women were more than twice as likely to have a CIN1 lesion diagnosed (age-adjusted relative risk, 2.09; 95% confidence interval [CI], 1.76–2.51) (Thiery et al., 2017).

Before the introduction of HPV testing, different screening intervals and ages were recommended in the USA and the Netherlands. Habbema et al. (2017) studied harms associated with cervical cancer screening and management of screen-positive women in the USA and the Netherlands. They included data on the number of Pap tests, abnormal test results, punch biopsies, treatments, and adverse effects of treatment (Table 4.1). The more intensive screening in the USA led to substantially higher rates of harms, with similar effects of screening on cervical cancer incidence and mortality in the two countries.

(b)   Overdiagnosis and overtreatment

The target lesion for detection in cervical screening is the precursor lesions (high-grade squamous intraepithelial lesion [HSIL]/AIS), and the preventive effect on cervical cancer incidence is through treatment of these lesions.

Downstaging of cervical cancers discovered via screening is a secondary benefit that may also contribute to reductions in cervical cancer mortality achieved through screening (see Section 4.1.1). Overdiagnosis is defined as the diagnosis of a cancer as a result of screening that would not have been diagnosed in the patient's lifetime if screening had not taken place. Harms related to overdiagnosis are caused both by the physical harms associated with treatment and by the psychosocial consequences of a cancer diagnosis. Some authors have argued that because not all CIN3 lesions will result in cancer in a woman's lifetime if left untreated, the diagnosis of CIN3 itself should be described as overdiagnosis (Malila et al., 2013; Hakama et al., 2015; van Luijt et al., 2016). However, because a significant proportion of CIN3 lesions will progress to invasive cancer (Braun et al., 2011) and it is not possible to know which lesions may be safely left untreated, the use of the term overdiagnosis in this context might have unintended effects and lead to a reduction in the treatment of women with CIN3 lesions, followed by a concomitant rise in cervical cancer rates (Paul et al., 2018).

Overtreatment is defined as the treatment of a lesion that would never have progressed to be clinically recognized during a woman's lifetime. In relation to cervical screening, precancerous lesions are asymptomatic and are only detected through screening or incidentally in the investigation of other gynaecological conditions. In cervical cancer screening, there is a potential for overtreatment because of false-positive results, misdiagnosis, and conservative overclassification of histopathology of a lower grade. Overtreatment also occurs when lesions with no malignant potential are identified as precancers (HSIL/AIS) that require treatment. HSIL encompasses both CIN2 and CIN3. Whereas CIN3 reliably represents transforming infection with malignant potential, CIN2 includes a mixture of lesions that indicate both florid productive infection and true transforming infection. Because of

an inability to reliably distinguish CIN2 lesions with true malignant potential from other lesions, most guidelines have recommended that CIN2 is also included as a treatment target (Arbyn et al., 2008b; Saslow et al., 2012; WHO, 2013; Jeronimo et al., 2016). However, the likelihood of progression from CIN2 to invasive cancer is lower than that of CIN3. The clinical course of untreated CIN2 at 24 months is 50% regression, 32% persistence, and 18% progression to CIN3 (Tainio et al., 2018). Methods of refining the diagnosis of CIN2 lesions so that the potential for progression can be better understood (e.g. through genotyping or molecular markers) may be strategies to reduce overtreatment. Age may also be a significant predictor of the likelihood of HSIL regression, because older women are less likely to experience regression of screen-detected lesions (Bekos et al., 2018). As described in Sections 1.2.1 and 1.2.2, the likelihood of a given lesion progressing to cancer will also be influenced by factors such as the causal HPV type, the woman's HIV status, and immunosuppression.

Overtreatment of CIN at grades below the accepted treatment thresholds may occur after referral due to abnormal cytology as part of the diagnostic process (e.g. via cone biopsy) or despite the availability of treatment guidelines (Volante et al., 2012; Nowakowski et al., 2016; Aitken et al., 2019).

References

Aitken CA, Siebers AG, Matthijsse SM, Jansen EEL, Bekkers RLM, Becker JH, et al. (2019). Management and treatment of cervical intraepithelial neoplasia in the Netherlands after referral for colposcopy. *Acta Obstet Gynecol Scand.* 98(6):737–46. doi:10.1111/aogs.13547 PMID:30687935

Akamatsu S, Kodama S, Himeji Y, Ikuta N, Shimagaki N (2012). A comparison of liquid-based cytology with conventional cytology in cervical cancer screening. *Acta Cytol.* 56(4):370–4. doi:10.1159/000337641 PMID:22846595

Alber JM, Brewer NT, Melvin C, Yackle A, Smith JS, Ko LK, et al. (2018). Reducing overuse of cervical cancer screening: a systematic review. *Prev Med.* 116:51–9. doi:10.1016/j.ypmed.2018.08.027 PMID:30149037

Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, et al. (2008). Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst.* 100(9):622–9. doi:10.1093/jnci/djn099 PMID:18445828

Anttila A (2007). Cervical cancer screening is effective – the Finnish experience. *Entre Nous.* 64:26–8. Available from: https://www.euro.who.int/__data/assets/pdf_file/0007/69766/en64.pdf.

Anttila A, von Karsa L, Aasmaa A, Fender M, Patnick J, Rebolj M, et al. (2009). Cervical cancer screening policies and coverage in Europe. *Eur J Cancer.* 45(15):2649–58. doi:10.1016/j.ejca.2009.07.020 PMID:19699081

Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al., editors (2008b). European guidelines for quality assurance in cervical cancer screening. 2nd ed. Luxembourg: Office for Official Publications of the European Communities.

Arbyn M, Sankaranarayanan R, Muwonge R, Keita N, Dolo A, Mbalawa CG, et al. (2008a). Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer.* 123(1):153–60. doi:10.1002/ijc.23489 PMID:18404671

Bekos C, Schwameis R, Heinze G, Gärner M, Grimm C, Joura E, et al. (2018). Influence of age on histologic outcome of cervical intraepithelial neoplasia during observational management: results from large cohort, systematic review, meta-analysis. *Sci Rep.* 8(1):6383. doi:10.1038/s41598-018-24882-2 PMID:29686397

Blatt AJ, Kennedy R, Luff RD, Austin RM, Rabin DS (2015). Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol.* 123(5):282–8. doi:10.1002/cncy.21544 PMID:25864682

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al.; STARD Group (2015). STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ.* 351:h5527. doi:10.1136/bmj.h5527 PMID:26511519

Braun S, Reimer D, Strobl I, Wieland U, Wiesbauer P, Müller-Holzner E, et al. (2011). Fatal invasive cervical cancer secondary to untreated cervical dysplasia: a case report. *J Med Case Reports.* 5(1):316. doi:10.1186/1752-1947-5-316 PMID:21767367

Bray F, Loos AH, McCarron P, Weiderpass E, Arbyn M, Møller H, et al. (2005). Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev.* 14(3):677–86. doi:10.1158/1055-9965.EPI-04-0569 PMID:15767349

Briët MC, Berger TH, van Ballegooijen M, Boon ME, Rebolj M (2010). Effects of streamlining cervical cancer screening the Dutch way: consequences of changes in the Dutch KOPAC-based follow-up protocol and consensus-based limitation of equivocal cytology. *Acta Cytol.* 54(6):1095–100. doi:10.1159/000325251 PMID:21428155

Castanon A, Leung VMW, Landy R, Lim AWW, Sasieni P (2013). Characteristics and screening history of women diagnosed with cervical cancer aged 20–29 years. *Br J Cancer.* 109(1):35–41. doi:10.1038/bjc.2013.322 PMID:23820257

Castle PE (2015). Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol.* 123(9):566. doi:10.1002/cncy.21572 PMID:26179787

Castle PE, Kinney WK, Xue X, Cheung LC, Gage JC, Poitras NE, et al. (2019). Role of screening history in clinical meaning and optimal management of positive cervical screening results. *J Natl Cancer Inst.* 111(8):820–7. doi:10.1093/jnci/djy192 PMID:30576462

Castle PE, Kinney WK, Xue X, Cheung LC, Gage JC, Zhao FH, et al. (2018). Effect of several negative rounds of human papillomavirus and cytology co-testing on safety against cervical cancer: an observational cohort study. *Ann Intern Med.* 168(1):20–9. doi:10.7326/M17-1609 PMID:29181509

Castle PE, Pierz AJ, Adcock R, Aslam S, Basu PS, Belinson JL, et al. (2020). A pooled analysis to compare the clinical characteristics of human papillomavirus-positive and -negative cervical precancers. *Cancer Prev Res (Phila).* 13(10):829–40. doi:10.1158/1940-6207.CAPR-20-0182 PMID:32655005

Chan KKL, Liu SS, Wei N, Ngu SF, Chu MMY, Tse KY, et al. (2020). Primary HPV testing with cytology versus cytology alone in cervical screening – a prospective randomized controlled trial with two rounds of screening in a Chinese population. *Int J Cancer.* 147(4):1152–62. doi:10.1002/ijc.32861 PMID:31922265

Clarke MA, Darragh TM, Nelson E, Unger ER, Zuna R, Cremer M, et al. (2020). Reporting and assessing the quality of diagnostic accuracy studies for cervical cancer screening and management. *J Low Genit Tract Dis.* 24(2):157–66. doi:10.1097/LGT.0000000000000527 PMID:32243311

FDA (2019). FDA executive summary. New approaches in the evaluation for high-risk human papillomavirus nucleic acid detection devices. Prepared for the March 8, 2019 meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/media/122799/download.

Forslund O, Elfström KM, Lamin H, Dillner J (2019). HPV-mRNA and HPV-DNA detection in samples taken up to seven years before severe dysplasia of cervix

uteri. *Int J Cancer*. 144(5):1073–81. doi:10.1002/ijc.31819 PMID:30125346

Giorgi Rossi P, Ronco G, Dillner J, Elfström KM, Snijders PJF, Arbyn M, et al.; New Technologies for Cervical Cancer Group (2016). Why follow-back studies should be interpreted cautiously: the case of an HPV-negative cervical lesion. *Cancer Cytopathol.* 124(1):66–7. doi:10.1002/cncy.21622 PMID:26356132

Habbema D, Weinmann S, Arbyn M, Kamineni A, Williams AE, de Kok IMCM, et al. (2017). Harms of cervical cancer screening in the United States and the Netherlands. *Int J Cancer*. 140(5):1215–22. doi:10.1002/ijc.30524 PMID:27864938

Hakama M, Pokhrel A, Malila N, Hakulinen T (2015). Sensitivity, effect and overdiagnosis in screening for cancers with detectable pre-invasive phase. *Int J Cancer*. 136(4):928–35. doi:10.1002/ijc.29053 PMID:24975995

Jeronimo J, Castle PE, Temin S, Denny L, Gupta V, Kim JJ, et al. (2016). Secondary prevention of cervical cancer: ASCO resource-stratified clinical practice guideline. *J Glob Oncol*. 3(5):635–57. doi:10.1200/JGO.2016.006577 PMID:29094101

Kaufman HW, Alagia DP, Chen Z, Onisko A, Austin RM (2020). Contributions of liquid-based (Papanicolaou) cytology and human papillomavirus testing in cotesting for detection of cervical cancer and precancer in the United States. *Am J Clin Pathol*. 154(4):510–6. doi:10.1093/ajcp/aqaa074 PMID:32637991

Kim JJ, Burger EA, Regan C, Sy S (2018). Screening for cervical cancer in primary care: a decision analysis for the US Preventive Services Task Force. *JAMA*. 320(7):706–14. doi:10.1001/jama.2017.19872 PMID:30140882

Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al. (2009). HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol*. 10(7):672–82. doi:10.1016/S1470-2045(09)70156-1 PMID:19540162

Landy R, Mathews C, Robertson M, Wiggins CL, McDonald YJ, Goldberg DW, et al. (2020). A statewide population-based evaluation of cervical cancers arising during opportunistic screening in the United States. *Gynecol Oncol*. 159(2):344–53. doi:10.1016/j.ygyno.2020.08.033 PMID:32977987

Leeflang MMG, Reitsma JB (2018). Systematic reviews and meta-analyses addressing comparative test accuracy questions. *Diagn Progn Res*. 2(1):17. doi:10.1186/s41512-018-0039-0 PMID:31093565

Leinonen MK, Nieminen P, Lönnberg S, Malila N, Hakama M, Pokhrel A, et al. (2012). Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. *BMJ*. 345:e7789. doi:10.1136/bmj.e7789 PMID:23197596

Maggino T, Sciarrone R, Murer B, Dei Rossi MR, Fedato C, Maran M, et al. (2016). Screening women for cervical cancer carcinoma with a HPV mRNA test: first results from the Venice pilot program. *Br J Cancer*. 115(5):525–32. doi:10.1038/bjc.2016.216 PMID:27490801

Malila N, Leinonen M, Kotaniemi-Talonen L, Laurila P, Tarkkanen J, Hakama M (2013). The HPV test has similar sensitivity but more overdiagnosis than the Pap test – a randomised health services study on cervical cancer screening in Finland. *Int J Cancer*. 132(9):2141–7. doi:10.1002/ijc.27850 PMID:22987601

Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al. (2007). Human papillomavirus and Papanicolaou tests to screen for cervical cancer. [Erratum in: N Engl J Med. 2008 359(15):1637. Johansson, Bo (added)] *N Engl J Med*. 357(16):1589–97. doi:10.1056/NEJMoa073204 PMID:17942872

Nowakowski A, Śliwczyński A, Seroczyński P, Cybulski M, Teter Z (2016). Reimbursed costs of management of uterine cervical lesions in Poland – a descriptive analysis of data from the National Health Fund and the Ministry of Health. *Cent Eur J Public Health*. 24(2):163–8. doi:10.21101/cejph.a4737 PMID:27178030

Odongua N, Chae YM, Kim MR, Yun JE, Jee SH (2007). Associations between smoking, screening, and death caused by cervical cancer in Korean women. *Yonsei Med J*. 48(2):192–200. doi:10.3349/ymj.2007.48.2.192 PMID:17461516

Ogilvie GS, van Niekerk D, Krajden M, Smith LW, Cook D, Gondara L, et al. (2018). Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA*. 320(1):43–52. doi:10.1001/jama.2018.7464 PMID:29971397

Paul C, Sharples KJ, Baranyai J, Jones RW, Skegg DC (2018). Outcomes for women without conventional treatment for stage 1A (microinvasive) carcinoma of the cervix. *Aust N Z J Obstet Gynaecol*. 58(3):321–9. doi:10.1111/ajo.12753 PMID:29405269

Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al.; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee (2020). 2019 ASCCP Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors. [Erratum in: J Low Genit Tract Dis. 2020 24(4):427] *J Low Genit Tract Dis*. 24(2):102–31. doi:10.1097/LGT.0000000000000525 PMID:32243307

Quinn M, Babb P, Jones J, Allen E; United Kingdom Association of Cancer Registries (1999). Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ*. 318(7188):904–8. doi:10.1136/bmj.318.7188.904 PMID:10102852

Rebolj M, Rask J, van Ballegooijen M, Kirschner B, Rozemeijer K, Bonde J, et al. (2015). Cervical histology after routine ThinPrep or SurePath liquid-based cytology and computer-assisted reading in Denmark. *Br J Cancer*. 113(9):1259–74. doi:10.1038/bjc.2015.339 PMID:26448176

Rebolj M, van Ballegooijen M, van Kemenade F, Looman C, Boer R, Habbema JDF (2008). No increased risk for cervical cancer after a broader definition of a negative Pap smear. *Int J Cancer*. 123(11):2632–5. doi:10.1002/ijc.23803 PMID:18767046

Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NWJ, Heideman DAM, et al. (2012). Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *Lancet Oncol*. 13(1):78–88. doi:10.1016/S1470-2045(11)70296-0 PMID:22177579

Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla Palma P, Naldoni C, et al. (2007). Accuracy of liquid based versus conventional cytology: overall results of New Technologies for Cervical Cancer Screening randomised controlled trial. *BMJ*. 335(7609):28. doi:10.1136/bmj.39196.740995.BE PMID:17517761

Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJF, Arbyn M, et al.; International HPV screening working group (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 383(9916):524–32. doi:10.1016/S0140-6736(13)62218-7 PMID:24192252

Ronco G, Franceschi S (2018). Cervical cancer screening: the transformational role of routine human papillomavirus testing. *Ann Intern Med*. 168(1):75–6. doi:10.7326/M17-2872 PMID:29181508

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al.; New Technologies for Cervical Cancer screening (NTCC) Working Group (2010). Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol*. 11(3):249–57. doi:10.1016/S1470-2045(09)70360-2 PMID:20089449

Ronco G, Pilutti S, Patriarca S, Montanari G, Ghiringhello B, Volante R, et al.; Turin Cervical Screening Working Group (2005). Impact of the introduction of organised screening for cervical cancer in Turin, Italy: cancer incidence by screening history 1992–98. *Br J Cancer*. 93(3):376–8. doi:10.1038/sj.bjc.6602705 PMID:16012518

Rozemeijer K, Naber SK, Penning C, Overbeek LIH, Looman CWN, de Kok IMCM, et al. (2017). Cervical cancer incidence after normal cytological sample in routine screening using SurePath, ThinPrep, and conventional cytology: population based study. *BMJ*. 356:j504. doi:10.1136/bmj.j504 PMID:28196844

Sander BB, Rebolj M, Lynge E (2014). Trends of cervical cancer in Greenland: a 60-year overview. *Acta Oncol*. 53(4):452–61. doi:10.3109/0284186X.2014.883462 PMID:24512341

Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. (2009). HPV screening for cervical cancer in rural India. *N Engl J Med*. 360(14):1385–94. doi:10.1056/NEJMoa0808516 PMID:19339719

Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al.; ACS-ASCCP-ASCP Cervical Cancer Guideline Committee (2012). American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin*. 62(3):147–72. doi:10.3322/caac.21139 PMID:22422631

Schiffman M, Wentzensen N (2021). Cervical screening performance. *Am J Clin Pathol*. 155(4):616–20. doi:10.1093/ajcp/aqaa198 PMID:33399187

Schwartz D, Lellouch J (1967). Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis*. 20(8):637–48. doi:10.1016/0021-9681(67)90041-0 PMID:4860352

Schwartz D, Lellouch J (2009). Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol*. 62(5):499–505. doi:10.1016/j.jclinepi.2009.01.012 PMID:19348976

Tainio K, Athanasiou A, Tikkinen KAO, Aaltonen R, Cárdenas Hernándes J, Glazer-Livson S, et al. (2018). Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ*. 360:k499. doi:10.1136/bmj.k499 PMID:29487049

Thiery A, Akladios C, Fender M, Severac F, Baldauf JJ (2017). Excess cervical cancer screening smears: any benefit? A retrospective cohort in Alsace, France. *J Med Screen*. 24(2):92–7. doi:10.1177/0969141316647091 PMID:27206814

van Luijt PA, Rozemeijer K, Naber SK, Heijnsdijk EAM, van Rosmalen J, van Ballegooijen M, et al. (2016). The role of pre-invasive disease in overdiagnosis: a microsimulation study comparing mass screening for breast cancer and cervical cancer. *J Med Screen*. 23(4):210–6. doi:10.1177/0969141316629505 PMID:27068430

Volante R, Giubilato P, Ronco G (2012). Cervical cancer screening in Italy: quality of colposcopy and treatment. 2010 activity. [in Italian] *Epidemiol Prev*. 36(6 Suppl 1):78–86. PMID:23293272

Wentzensen N, Walker JL, Gold MA, Smith KM, Zuna RE, Mathews C, et al. (2015). Multiple biopsies and detection of cervical cancer precursors at colposcopy. *J Clin Oncol*. 33(1):83–9. doi:10.1200/JCO.2014.55.9948 PMID:25422481

WHO (2013). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/94830; https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/.

ZORA (2018). National Cervical Cancer Screening Programme ZORA. Ljubljana, Slovenia: Cervical Cancer Screening Program and Registry ZORA. [in Slovenian] Available from: https://zora.onko-i.si/publikacije/kazalniki/.

Zorzi M, Del Mistro A, Giorgi Rossi P, Laurino L, Battagello J, Lorio M, et al. (2020). Risk of CIN2 or more severe lesions after negative HPV-mRNA E6/E7 overexpression assay and after negative HPV-DNA test: concurrent cohorts with a 5-year follow-up. *Int J Cancer*. 146(11):3114–23. doi:10.1002/ijc.32695 PMID:31583683

4.2 Screening by visual inspection

4.2.1 Visual inspection techniques

Visual techniques used in cervical screening include naked-eye examination with acetic acid (VIA) or Lugol's iodine (VILI) and camera-enhanced visual inspection. Naked-eye examination (with VIA or VILI) is a simple test for the early detection of cervical precancerous lesions and early invasive cancer and has been widely used in low- and middle-income countries (LMICs) to screen women for cervical precancer (Sankaranarayanan et al., 1998; Sankaranarayanan & Wesley, 2003). More recently, camera-enhanced image capture has been used to improve the performance of VIA (e.g. digital cervicography, smartphone attachments, intravaginal endoscopes, and portable monoscopic devices) (Parham et al., 2015; Goldstein et al., 2020; Xue et al., 2020) (see also Section 4.6.1). To date, no large randomized controlled trials (RCTs) have been performed that would enable the objective assessment of the effectiveness of enhanced VIA systems to detect precancer compared with routine VIA.

Recently, the combination of related novel technologies has enabled the development of artificial intelligence (AI) devices, which may supersede current technologies (see Section 4.6.1).

(a) Description of procedures

Visual inspection is appropriate for use in women in whom the squamocolumnar junction (SCJ) is visible (typically those younger than 50 years). In older, postmenopausal women, the SCJ gradually recedes into the endocervical canal, and it is possible to miss lesions when relying on visual inspection. Similarly, visual inspection cannot be used in younger women with a type 3 transformation zone (TZ). Therefore, before visual inspection is performed, the TZ type first needs to be accurately assessed (see Section 1.2.5, Fig. 1.18).

(i) Visual inspection with acetic acid (VIA)

Acetic acid causes dehydration of the cells of the cervical epithelium and some surface coagulation of cellular proteins, which reduces the transparency of the epithelium. These changes are more pronounced in abnormal epithelium, because of the higher nuclear density and consequent high concentration of proteins (Sankaranarayanan et al., 1998). After the application of acetic acid, more light is reflected back, making the epithelium appear white. The cervix is viewed with the naked eye through a vaginal speculum with the patient in either the left lateral position (dorsal with legs flexed) or the lithotomy position. VIA requires a good light source and freshly prepared 3–5% acetic acid in distilled water, and the examination should be carried out by a trained health-care provider (Sankaranarayanan & Wesley, 2003; WHO, 2014).

After gently removing any mucus from the cervix, the provider applies the acetic acid solution using a soaked swab or a spray bottle, and then looks to see if any white changes appear. The results of VIA examination are categorized as negative, positive, or suspicious for cancer (Table 4.2; Sankaranarayanan & Wesley, 2003; WHO, 2017). Acetowhite changes on the cervix that do not recede after 1 minute are likely to be associated with cervical precancer or cancer. If these changes are seen in the TZ and have well-defined borders, it is considered a positive result (WHO, 2013a, 2014). A positive VIA test result will reveal an area or areas of intense acetic acid uptake with distinct margins, usually close to or arising from the SCJ. If the TZ is fully visible, a woman with a positive VIA test result can be treated immediately with cryotherapy or thermal ablation, subject to certain requirements, in a single-visit screen-and-treat approach (see Section 5.1; WHO, 2013a, 2019), or may be referred for triage with colposcopy and treated in the conventional manner.

Table 4.2 Categories of results of visual inspection with acetic acid (VIA) examination

Test result	Clinical findings 1 minute after application of 3–5% acetic acid
Negative	No acetowhite lesions or faint acetowhite lesions due to squamous metaplasia or regenerating epithelium, cervicitis, inflammation; acetowhitening of polyps, Nabothian cysts; acetowhitening of the SCJ; satellite acetowhite lesions far away from the SCJ
Positive	Sharp, distinct, well-defined, dense (opaque/dull or oyster white) acetowhite area with or without raised margins touching the SCJ; leukoplakia and warts
Suspicious for cancer	Large chalky white acetowhite lesions obliterating the endocervical canal with irregular surface and raised and rolled-out margins; bleeding on touch; clinically visible ulcerative, cauliflower-like growth or ulcer

SCJ, squamocolumnar junction.
Table compiled by the Working Group.

VIA positivity rates vary considerably, partly because of the intrinsic subjectivity of the method (Almonte et al., 2015). The diagnostic accuracy of VIA has been shown to be variable and dependent on several factors, including the training and experience of the test provider, the adequacy of the light source, the concentration of acetic acid used, participant characteristics such as age (Castle et al., 2014; Raifu et al., 2017), the presence of infection with carcinogenic HPV types (Castle et al., 2014), and coexisting cervical inflammation (see Section 4.2.2).

(ii) Visual inspection with Lugol's iodine (VILI)

Lugol's iodine (5%) is relatively expensive. It can be prepared locally and should be discarded after 3–6 months. VILI may also be used as an adjunct to VIA and as an aid to precise treatment. Normal mature squamous epithelium takes up iodine and becomes a mahogany brown colour because of its high glycogen content. Dysplastic, metaplastic, and glandular epithelial tissues have minimal or no glycogen and do not take up iodine; they appear as well-defined, thick, mustard or saffron yellow areas. For women indicated for treatment, Lugol's iodine is valuable in demarcating the outer limit of the TZ, enabling the size of the TZ to be estimated so that the dimensions of the probe or the number of applications to be used can be calculated. Lugol's

iodine is also a reasonably effective antiseptic agent (Sankaranarayanan & Wesley, 2003).

As observed for VIA, VILI has variable sensitivity, ranging from 50% (95% CI, 31–69%) to 100% (95% CI, 70–100%), and specificity, ranging from 69% (95% CI, 68–70%) to 97% (95% CI, 97–98%), for precancerous lesions (Catarino et al., 2018). In studies that evaluated VIA and VILI in head-to-head comparisons, the sensitivity of VILI for CIN2+ was higher than that of VIA (relative sensitivity, 1.11; 95% CI, 1.06–1.16), without significant loss in specificity (relative specificity, 0.98; 95% CI, 0.95–1.01). The higher sensitivity of VILI may be because the colour changes produced by the application of Lugol's iodine are more apparent visually than the whitening observed after the application of acetic acid.

(b) Strengths and limitations

The strengths and limitations of cervical screening using VIA are summarized in Table 4.3. Naked-eye examination of the cervix with acetic acid and/or Lugol's iodine as a means of detecting cervical precancer arose because of the absence or suboptimal performance of the screening methods used in high-income countries (i.e. cytology followed by colposcopy) when used in LMICs. VIA and VILI have several advantages. Any type of health-care worker can perform the test, and the results are available

Table 4.3 Strengths and limitations of cervical screening using visual inspection with acetic acid (VIA)

Strengths	Limitations
Simple, affordable, safe, and easy to learn and practise clinical testing, which requires minimal infrastructure and no or minimal laboratory support	Provider-dependent test outcome
Acetic acid is widely available and affordable	Test accuracy, particularly sensitivity, is highly variable in different settings and is dependent on training, supervision, and regular quality assurance
Different categories of health-care providers can learn and perform VIA	No standardized training and quality assurance methods for ensuring provider competency
Rapid, real-time test with immediately available test results, which enables a single-visit screen-and-treat approach or immediate triage with colposcopy or colposcopy-directed biopsy	Less accurate in postmenopausal women, because the SCJ recedes into the endocervical canal with increasing age
Low start-up and sustaining costs, which may enable use of the VIA screen-and-treat approach in primary care services	Moderate to low specificity to distinguish CIN2+ leads to resources being spent on unnecessary treatment of women who are free of precancerous lesions in a single-visit approach; leads to unnecessary investigations, such as colposcopy or biopsy, in settings where triage in VIA-positive women is done. Variable sensitivity leads to some women with CIN2+ or CIN3+ being incorrectly classified as disease-free
Focused visualization of the cervix enables early diagnosis of preclinical, asymptomatic early cervical cancer	Health and cost implications of overtreatment because of low specificity and/or missed cases because of low sensitivity

CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; SCJ, squamocolumnar junction; VIA, visual inspection with acetic acid.
Table compiled by the Working Group.

immediately, which enables a screen-and-treat protocol. The tests are laboratory-independent and inexpensive. Finally, a screening programme established using naked-eye examination will familiarize women and health-care providers with the concept of cancer prevention. VIA was formally endorsed by WHO in 2013 as a legitimate means of screening, particularly as part of a screen-and-treat approach in LMICs (WHO, 2013a). The application of 3% or 5% acetic acid is also used in some regions to determine eligibility for ablative treatment in women with a positive HPV test result, and also to determine the site, size, and type of the TZ.

The primary problem with naked-eye techniques is that they are highly subjective and consequently have variable sensitivity and specificity to detect precancer. Quality control and quality assurance for visual screening are important to maintain uniform and reproducible criteria for test positivity, and to ensure that the provider accurately differentiates between true-positive and true-negative cases (WHO, 2013b). Ensuring adequate training, supervision, and continuing quality assurance can be challenging in practice. Furthermore, visual examinations are an assessment of the ectocervical epithelium and cannot detect either glandular disease or endocervical squamous disease. In perimenopausal and postmenopausal women, the SCJ recedes into the endocervical canal and thus cannot be adequately observed with naked-eye examination. Even a proportion of women of reproductive age have a TZ of type 2 or 3 (see Fig. 1.18).

Table 4.4 Pooled sensitivity and specificity of visual inspection with acetic acid (VIA) to detect CIN2+ lesions

Reference	Study population Reference standard	Pooled sensitivity (%) (95% CI)	Pooled specificity (%) (95% CI)
Arbyn et al. (2008)	58 679 women from 11 studies Colposcopy with or without biopsy	79 (73–85)	85 (81–89)
Zhao et al. (2010)	28 848 women from 17 studies Four-quadrant biopsies	48 (42–54)	90 (87–94)
Chen et al. (2012)	99 972 women from 22 studies Colposcopy with or without biopsy	77 (75–78)	87 (87–88)
Bobdey et al. (2015)	57 225 women from 11 studies Colposcopy with or without biopsy	69 (32–100)	84 (53–91)
Fokom-Domgue et al. (2015)	61 381 women from 15 studies Colposcopy with or without biopsy	82 (76–87)	87 (78–93)
Adsul et al. (2017)	313 553 women from 20 studies Colposcopy with or without biopsy	17–83[a]	82–97[a]
Catarino et al. (2018)	101 273 women from 23 studies Colposcopy followed by colposcopy-directed biopsy or excision biopsy	78 (73–83)	88 (85–91)

CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse.

[a] Range in included studies; pooled estimates are not presented.

(c) Quality assurance for VIA

Quality assurance includes (but is not limited to) competency-based training of VIA providers, supervision, periodic refresher training, evaluation of current programme activities and long-term impact, a mechanism for constructive feedback from women and health-care providers, and an effective information system (see also Section 2.3). Training requirements for VIA providers are highly variable; WHO recommends a 10-day training (WHO, 2017), but in different programmatic settings the duration of training varies between 5 days and a few months (Blumenthal et al., 2005). Training is mainly non-standardized and is one of the weakest components of VIA screening initiatives. Some training manuals are available, which have been adapted by many countries (Sankaranarayanan & Wesley, 2003; WHO, 2013a, 2017), and a guide for quality control and quality assurance for VIA-based programmes has been published by WHO (WHO, 2013b).

4.2.2 Beneficial effects of screening using VIA

(a) Accuracy of VIA screening

VIA has been evaluated for its accuracy to detect CIN2+ lesions in cross-sectional studies in various settings in Africa, Asia, and Latin America. In most of these studies, the diagnostic reference standard used to establish the final diagnosis was colposcopy plus colposcopy-directed biopsy (Table 4.4), although some studies in China used four-quadrant biopsies to establish the final diagnosis (Belinson et al., 2001; Zhao et al., 2010, 2020; Holt et al., 2017). In studies that relied on colposcopy as the reference standard, no biopsies were directed when no colposcopic abnormalities were detected; directed biopsies were reserved for women with colposcopic abnormalities. In some studies the reference standard was used for all cases, thereby eliminating verification bias to a large extent, whereas in other studies the reference standard was used for all screen-positive women plus a proportion of screen-negative women. When the colposcopic

impression did not suggest precancer, no biopsy was taken, and this outcome was accepted as absence of precancer. [Given that standard colposcopy can miss up to 40.0% of prevalent precancers (Wentzensen et al., 2015), and given the inherent verification bias in studies and the close correlation of colposcopy with visual screening approaches, the reported sensitivity estimates of VIA are likely to be inflated.]

There is wide variation in VIA positivity rates across studies, from 1% to 36%. This indicates that VIA performance is subjective and depends on the study and the provider; there is little reproducibility, and provider training and thresholds used for test positivity vary (Jeronimo et al., 2014; Shastri et al., 2014; Huchko et al., 2015a, b; Poli et al., 2015).

In meta-analyses, the pooled sensitivity of VIA to detect CIN2+ lesions ranged from 48% to 83%, and the pooled specificity varied from 84% to 97% (Table 4.4). The sensitivity of VIA declines substantially in postmenopausal women. In a pooled analysis of 17 population-based studies in postmenopausal women, the sensitivity of VIA to detect CIN2+ lesions was 31.0% (95% CI, 21.8–41.4%) and the specificity was 94.6% (93.7–95.4%) (Holt et al., 2017). [The interpretation of VIA in perimenopausal and postmenopausal women is challenging, because the epithelium is pale, degenerated, and brittle and it bleeds on touch, and the TZ is partially visible or not visible. Given the methodological limitations, estimates of the absolute accuracy of VIA should be interpreted with caution.] It has been shown that low-level magnification does not improve the performance of naked-eye VIA (Basu et al., 2003; Sankaranarayanan et al., 2004; Shastri et al., 2005; Chen et al., 2012; Bobdey et al., 2015). Variation in test positivity is partly responsible for the varying accuracy of VIA in detecting high-grade lesions; the quality of the diagnostic reference standard used in different settings, which is also highly variable, is another factor that determines the variability of accuracy estimates (Sankaranarayanan et al., 2012).

HIV-positive women have a higher prevalence of HPV infection and a higher incidence of cervical cancer compared with HIV-negative women, partly because of the modifying effect of HIV on HPV pathogenesis (see Section 5.2.1). The screening methods used for HIV-seropositive women are the same as those used for HIV-negative women, with varying clinical performance and accuracy. In HIV-positive women, the use of VIA to detect CIN2+ had a sensitivity of 48.0–80.0% and a specificity of 65.0–92.0% (Ghebre et al., 2017; Mapanga et al., 2018). Visual screening tests might be expected to perform better in HIV-positive women than in the general population, because of the higher prevalence of high-grade lesions and the possibility of large lesions in HIV-positive women (Sahasrabuddhe et al., 2012; Joshi et al., 2013), although a high prevalence of HPV infection and other infections as well as inflammation may adversely affect the specificity of VIA.

(b) Cervical cancer incidence and mortality

VIA screening has been evaluated for its effect on cervical cancer incidence and/or mortality compared with control populations receiving usual care (very low prevalence of screening) in three large cluster-randomized trials in India (Sankaranarayanan et al., 2007, 2009; Shastri et al., 2014). The cervical cancer incidence rates, the detection rates of CIN2+ lesions, and the cervical cancer mortality rates in the VIA and control groups are given in Table 4.5. VIA positivity rates ranged from 2% (Shastri et al., 2014) to 13.9% (Sankaranarayanan et al., 2009), which indicates the subjective nature of VIA interpretation, differences in training and quality assurance, and possibly different thresholds used for VIA positivity.

In the study in Dindigul District, India, the intervention was a single round of VIA by trained nurses (Sankaranarayanan et al., 2007).

Table 4.5 Detection rates of CIN2/CIN3 lesions and cervical cancer incidence and mortality rates in randomized trials of screening with visual inspection with acetic acid (VIA)

Reference Study design	Cervical cancer incidence rate per 100 000 person-years		Detection rate of CIN2/CIN3 lesions per 1000 women invited		Screen-negative cervical cancer incidence rate per 100 000 person-years	Cervical cancer mortality rate per 100 000 person-years	
	VIA group	Control group	VIA group	Control group		VIA group	Control group
Sankaranarayanan et al. (2007) 49 311 women aged 30–59 yr in the VIA group and 30 958 women in the control group; single round of VIA screening by nurses	75.2[a]	99.1[a]	4.84	NA	NA	39.6[a]	56.7[a]
Sankaranarayanan et al. (2009) 34 074 women aged 30–59 yr in the VIA group and 31 488 women in the control group; single round of VIA screening by trained auxiliary-nurse midwives	58.7[a]	47.6[a]	5.72	0.48	16.0[b]	20.9[a]	25.8[a]
Shastri et al. (2014) 75 360 women aged 30–64 yr in the VIA group and 76 178 women in the control group; 4 rounds of VIA at 2-yr intervals by primary health workers	29.0[a]	29.4[a]	1.44	0.17	NA	14.4[a]	19.8[a]

CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; NA, not available; VIA, visual inspection with acetic acid; yr, year or years.

[a] Standardized rate using world standard population.

[b] Invasive cervical cancer.

The study involved women aged 30–59 years, with 49 311 in the VIA group and 30 958 in the control group. Of the 3088 (9.9%) women with a positive test result on VIA, 3052 (98.9%) underwent colposcopy and 2539 (82.2%) had directed biopsy. Of the 1874 women with precancerous lesions, 72.0% received treatment. During 2000–2006, in the VIA group, for 274 430 person-years, 167 cervical cancer cases and 83 cervical cancer deaths were recorded, whereas in the control group, for 178 781 person-years, 158 cervical cancer cases and 92 cervical cancer deaths were recorded (incidence hazard ratio, 0.75; 95% CI, 0.55–0.95; mortality hazard ratio, 0.65; 95% CI, 0.47–0.89). The Dindigul District study was the first randomized trial of VIA screening to report

a significant reduction in cervical cancer incidence and mortality after VIA screening.

In the study in Osmanabad District, India, a single round of VIA was administered by trained paramedical workers (Sankaranarayanan et al., 2009). The study involved women aged 30–59 years, with 34 074 in the VIA group and 31 488 in the control group. In the VIA group, the VIA positivity rate was 13.9%; this decreased from 17.8% in women aged 30–39 years to 6.4% in women aged 50–59 years. In the VIA group, 195 women with CIN2 and CIN3 lesions, 157 cervical cancers, and 56 cervical cancer deaths were recorded, whereas in the control group 15 women with CIN2 and CIN3 lesions, 118 cervical cancers, and 64 cervical cancer deaths were recorded (incidence hazard ratio, 1.30; 95% CI,

0.95–1.78; mortality hazard ratio, 0.86; 95% CI, 0.60–1.25) (Sankaranarayanan et al., 2009).

[The differing results for VIA screening in the two above-mentioned studies may be due to a lack of power to detect a significant reduction in mortality in the Osmanabad District study and the higher frequency of treatment of precancerous lesions in the Dindigul District study. In the Osmanabad District study, screening with HPV testing was associated with a significant reduction in advanced disease and mortality, indicating a better accuracy to detect precancerous lesions.]

The third trial, in Mumbai, evaluated four rounds of VIA screening provided by trained primary health workers every 2 years (Shastri et al., 2014). The VIA positivity rate varied from 1.3% to 2.5%. This study recruited 75 360 women aged 30–64 years from 10 clusters in the VIA group and 76 178 women from 10 comparable clusters in the control group. A significant 31% reduction in cervical cancer mortality (incidence rate ratio [IRR], 0.69; 95% CI, 0.54–0.88; $P = 0.003$) and a non-significant 7% reduction in all-cause mortality (mortality IRR, 0.93; 95% CI, 0.79–1.10; $P = 0.41$) was associated with VIA screening compared with the control group, but no reduction in the incidence of cervical cancer was observed (IRR, 0.97; 95% CI, 0.80–1.19; $P = 0.79$). [The low detection rate of high-grade lesions, possibly as a consequence of low VIA positivity rates (1.3–2.5%) in the four rounds of VIA screening, along with stage shift of invasive cancers, possibly led to the reduction in mortality only rather than reductions in both incidence and mortality in the Mumbai trial.

(c)   Single-visit VIA screen-and-treat approach

In an RCT in women aged 35–65 years in South Africa, HPV DNA screen-and-treat (2163 women) and VIA screen-and-treat (2227 women) protocols were compared with a delayed-evaluation group (2165 women). At 6 months after randomization, the prevalence of CIN2+ lesions

was significantly lower in the two screen-and-treat groups than in the delayed-evaluation group (Denny et al., 2005). In both screened groups, 22% of women underwent cryotherapy. At 6 months, CIN2+ lesions were detected in 2.23% (95% CI, 1.57–2.89%) of women in the VIA group compared with 3.55% (95% CI, 2.71–4.39%) of women in the delayed-evaluation group ($P = 0.02$); in the HPV DNA group, CIN2+ lesions were detected in 0.80% (95% CI, 0.40–1.20%) of women. At 12 months, the cumulative prevalence of CIN2+ lesions in a subset of women was 2.91% (95% CI, 2.12–3.69%) in the VIA group and 5.41% (95% CI, 4.32–6.50%) in the delayed-evaluation group; in the HPV DNA group, the cumulative prevalence of CIN2+ lesions was 1.42% (95% CI, 0.87–1.97%). There were no differences in HIV seroconversion rates 6 months after randomization; this was reassuring about possible virus transmission during screen-and-treat procedures, but the study was underpowered to detect small increases.

4.2.3 Harms of screening using VIA

Although VIA has been evaluated for its performance in cross-sectional studies in Africa, Asia, and Latin America and has been implemented opportunistically as a point-of-care screening approach or in programmes, there is very little systematic documentation of associated harms (Muwonge et al., 2010; Poli et al., 2015). Given the simplicity of VIA as a screening procedure, the innocuous nature of acetic acid, and the lack of documentation of serious adverse events in studies, VIA is assumed to be safe. A few studies have documented the rate of important potential harms, including adverse reproductive outcomes (from treatment) and complications that can be directly attributed to VIA, although the evidence is of low quality (Fokom-Domgue et al., 2014). Arguably the major risk of VIA as a screening test is that it will not always recognize

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Box 4.1 Harms of visual screening

- Physical harms associated with true-positive test results (i.e. accurate screening, correct diagnosis and treatment):
  - pain and discomfort during screening and treatment
  - discharge, pain, bleeding, and infection risk after treatment
  - long-term treatment complications (premature labour, threatened miscarriage, and cervical stenosis)
- Psychological harms:
  - periprocedural anxiety
  - psychological stress and fear of pelvic examination, VIA screening, and downstream procedures of diagnosis, treatment, and follow-up care
- Harms associated with false-positive test results:
  - unnecessary investigations (if triage of women with a positive test result is done)
  - unnecessary biopsy
  - overtreatment (with attendant risk of short-term and long-term physical harms as detailed above)
  - costs of unnecessary medical care
- False reassurance and risk of future cervical neoplasia because of a false-negative test result
- Harms associated with overdiagnosis

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an endocervical TZ and thus may falsely reassure a woman that she does not have precancer when in fact she does.

(a) Physical harms

There is very little documentation of either immediate physical harm (such as bleeding, pain and irritation due to insertion of the speculum, lower abdominal cramps, syncope, febrile illness, or allergic reactions) or late adverse events (such as delayed bleeding, cervicitis, cervical ulceration, pelvic inflammatory disease, pregnancy loss, preterm labour, or cervical stenosis) from examination with VIA.

Given the well-documented limitations in the accuracy of VIA, there are likely to be harms from overtreatment of women with false-positive test results (Parra et al., 2020), particularly in the screen-and-treat setting, as well as the potentially serious harm of a failure to detect a lesion that may develop into invasive cancer (false-negative test result). Potential harms of false-positive and false-negative test results are given in Box 4.1. False-positive test results lead to unnecessary investigations and costs of unnecessary medical care (in settings using triage with colposcopy of women with a positive test result), unnecessary biopsy, and harms associated with treatment, such as excessive discharge, risks of bleeding, infection and pelvic inflammatory disease, and long-term sequelae such as premature labour, threatened miscarriage, and cervical stenosis. [Variations in the accuracy of visual screening are caused by variations in the performance of VIA providers rather than underlying variations in the prevalence of disease; this indicates

that harms associated with VIA can be reduced if providers are well trained in the procedure (Raifu et al., 2017).]

(b) Psychological harms

Psychological harms include anxiety and fear caused by the procedure itself and by a positive test result, and the stress associated with making the decision to accept screen-and-treat in the same session (in a single-visit approach) and to give consent for eligibility determination and treatment procedures. Women undergoing pelvic examination can experience anxiety, fear, and embarrassment, and the associated stress can lead to exacerbation of procedure-related discomfort, which may discourage women from undergoing the procedure and may induce low patient compliance (Galaal et al., 2011; O'Connor et al., 2016a, b; Vorsters et al., 2017). In one study in Cameroon, enabling women to watch the VIA procedure on a digital screen in real time improved their emotional state but did not reduce periprocedural anxiety as measured by the Spielberger State-Trait Anxiety Inventory (STAI) score (Camail et al., 2019).

References

Adsul P, Manjunath N, Srinivas V, Arun A, Madhivanan P (2017). Implementing community-based cervical cancer screening programs using visual inspection with acetic acid in India: a systematic review. *Cancer Epidemiol*. 49:161–74. doi:10.1016/j.canep.2017.06.008 PMID:28704717

Almonte M, Ferreccio C, Luciani S, Gonzales M, Delgado JM, Santos C, et al. (2015). Visual inspection after acetic acid (VIA) is highly heterogeneous in primary cervical screening in Amazonian Peru. *PLoS One*. 10(1):e0115355. doi:10.1371/journal.pone.0115355 PMID:25635965

Arbyn M, Sankaranarayanan R, Muwonge R, Keita N, Dolo A, Mbalawa CG, et al. (2008). Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer*. 123(1):153–60. doi:10.1002/ijc.23489 PMID:18404671

Basu PS, Sankaranarayanan R, Mandal R, Roy C, Das P, Choudhury D, et al.; Calcutta Cervical Cancer Early Detection Group (2003). Visual inspection with acetic acid and cytology in the early detection of cervical neoplasia in Kolkata, India. *Int J Gynecol Cancer*. 13(5):626–32. doi:10.1136/ijgc-00009577-200309000-00009 PMID:14675346

Belinson J, Qiao YL, Pretorius R, Zhang WH, Elson P, Li L, et al. (2001). Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. [Erratum in: Gynecol Oncol. 2002 84(2):355] *Gynecol Oncol*. 83(2):439–44. doi:10.1006/gyno.2001.6370 PMID:11606114

Blumenthal PD, Lauterbach M, Sellors JW, Sankaranarayanan R (2005). Training for cervical cancer prevention programs in low-resource settings: focus on visual inspection with acetic acid and cryotherapy. *Int J Gynaecol Obstet*. 89(Suppl 2):S30–7. doi:10.1016/j.ijgo.2005.01.012 PMID:15823264

Bobdey S, Balasubramanium G, Kumar A, Jain A (2015). Cancer screening: should cancer screening be essential component of primary health care in developing countries? *Int J Prev Med*. 6:56. PMID:26236443

Camail R, Kenfack B, Tran PL, Viviano M, Tebeu PM, Temogne L, et al. (2019). Benefit of watching a live visual inspection of the cervix with acetic acid and Lugol iodine on women's anxiety: randomized controlled trial of an educational intervention conducted in a low-resource setting. *JMIR Cancer*. 5(1):e9798. doi:10.2196/cancer.9798 PMID:31094335

Castle PE, Qiao YL, Zhao FH, Chen W, Valdez M, Zhang X, et al. (2014). Clinical determinants of a positive visual inspection after treatment with acetic acid for cervical cancer screening. *BJOG*. 121(6):739–46. doi:10.1111/1471-0528.12646 PMID:24575872

Catarino R, Schäfer S, Vassilakos P, Petignat P, Arbyn M (2018). Accuracy of combinations of visual inspection using acetic acid or Lugol iodine to detect cervical precancer: a meta-analysis. *BJOG*. 125(5):545–53. doi:10.1111/1471-0528.14783 PMID:28603909

Chen C, Yang Z, Li Z, Li L (2012). Accuracy of several cervical screening strategies for early detection of cervical cancer: a meta-analysis. *Int J Gynecol Cancer*. 22(6):908–21. doi:10.1097/IGC.0b013e318256e5e4 PMID:22672987

Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC Jr (2005). Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA*. 294(17):2173–81. doi:10.1001/jama.294.17.2173 PMID:16264158

Fokom-Domgue J, Combescure C, Fokom-Defo V, Tebeu PM, Vassilakos P, Kengne AP, et al. (2015). Performance of alternative strategies for primary cervical cancer screening in sub-Saharan Africa: systematic review and meta-analysis of diagnostic

test accuracy studies. *BMJ*. 351:h3084. doi:10.1136/bmj.h3084 PMID:26142020

Fokom-Domgue J, Vassilakos P, Petignat P (2014). Is screen-and-treat approach suited for screening and management of precancerous cervical lesions in sub-Saharan Africa? *Prev Med*. 65:138–40. doi:10.1016/j.ypmed.2014.05.014 PMID:24879892

Galaal K, Bryant A, Deane KHO, Al-Khaduri M, Lopes AD (2011). Interventions for reducing anxiety in women undergoing colposcopy. *Cochrane Database Syst Rev*. (12):CD006013. doi:10.1002/14651858.CD006013.pub3 PMID:22161395

Ghebre RG, Grover S, Xu MJ, Chuang LT, Simonds H (2017). Cervical cancer control in HIV-infected women: past, present and future. *Gynecol Oncol Rep*. 21:101–8. doi:10.1016/j.gore.2017.07.009 PMID:28819634

Goldstein A, Goldstein LS, Lipson R, Bedell S, Wang J, Stamper SA, et al. (2020). Assessing the feasibility of a rapid, high-volume cervical cancer screening programme using HPV self-sampling and digital colposcopy in rural regions of Yunnan, China. *BMJ Open*. 10(3):e035153. doi:10.1136/bmjopen-2019-035153 PMID:32234744

Holt HK, Zhang L, Zhao FH, Hu SY, Zhao XL, Zhang X, et al. (2017). Evaluation of multiple primary and combination screening strategies in postmenopausal women for detection of cervical cancer in China. *Int J Cancer*. 140(3):544–54. doi:10.1002/ijc.30468 PMID:27727464

Huchko MJ, Sneden J, Sawaya G, Smith-McCune K, Maloba M, Abdulrahim N, et al. (2015a). Accuracy of visual inspection with acetic acid to detect cervical cancer precursors among HIV-infected women in Kenya. *Int J Cancer*. 136(2):392–8. doi:10.1002/ijc.28996 PMID:24889387

Huchko MJ, Sneden J, Zakaras JM, Smith-McCune K, Sawaya G, Maloba M, et al. (2015b). A randomized trial comparing the diagnostic accuracy of visual inspection with acetic acid to visual inspection with Lugol's iodine for cervical cancer screening in HIV-infected women. *PLoS One*. 10(4):e0118568. doi:10.1371/journal.pone.0118568 PMID:25849627

Jeronimo J, Bansil P, Lim J, Peck R, Paul P, Amador JJ, et al.; START-UP Study Group (2014). A multicountry evaluation of careHPV testing, visual inspection with acetic acid, and Papanicolaou testing for the detection of cervical cancer. *Int J Gynecol Cancer*. 24(3):576–85. doi:10.1097/IGC.0000000000000084 PMID:24557438

Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U (2013). Screening of cervical neoplasia in HIV-infected women in India. *AIDS*. 27(4):607–15. doi:10.1097/QAD.0b013e32835b1041 PMID:23079814

Mapanga W, Girdler-Brown B, Feresu SA, Chipato T, Singh E (2018). Prevention of cervical cancer in HIV-seropositive women from developing countries through cervical cancer screening: a systematic review.

Syst Rev. 7(1):198. doi:10.1186/s13643-018-0874-7 PMID:30447695

Muwonge R, Manuel MG, Filipe AP, Dumas JB, Frank MR, Sankaranarayanan R (2010). Visual screening for early detection of cervical neoplasia in Angola. *Int J Gynaecol Obstet*. 111(1):68–72. doi:10.1016/j.ijgo.2010.04.024 PMID:20570259

O'Connor M, Gallagher P, Waller J, Martin CM, O'Leary JJ, Sharp L; Irish Cervical Screening Research Consortium (CERVIVA) (2016b). Adverse psychological outcomes following colposcopy and related procedures: a systematic review. *BJOG*. 123(1):24–38. doi:10.1111/1471-0528.13462 PMID:26099164

O'Connor M, O'Leary E, Waller J, Gallagher P, D'arcy T, Flannelly G, et al.; Irish Cervical Screening Research Consortium (CERVIVA) (2016a). Trends in, and predictors of, anxiety and specific worries following colposcopy: a 12-month longitudinal study. *Psychooncology*. 25(5):597–604. doi:10.1002/pon.3980 PMID:26392040

Parham GP, Mwanahamuntu MH, Kapambwe S, Muwonge R, Bateman AC, Blevins M, et al. (2015). Population-level scale-up of cervical cancer prevention services in a low-resource setting: development, implementation, and evaluation of the cervical cancer prevention program in Zambia. *PLoS One*. 10(4):e0122169. doi:10.1371/journal.pone.0122169 PMID:25885821

Parra SG, López-Orellana LM, Molina Duque AR, Carns JL, Schwarz RA, Smith CA, et al. (2020). Cervical cancer prevention in El Salvador: a prospective evaluation of screening and triage strategies incorporating high-resolution microendoscopy to detect cervical precancer. *Int J Cancer*. doi:10.1002/ijc.33454 PMID:33368249

Poli UR, Bidinger PD, Gowrishankar S (2015). Visual inspection with acetic acid (VIA) screening program: 7 years experience in early detection of cervical cancer and pre-cancers in rural south India. *Indian J Community Med*. 40(3):203–7. doi:10.4103/0970-0218.158873 PMID:26170547

Raifu AO, El-Zein M, Sangwa-Lugoma G, Ramanakumar A, Walter SD, Franco EL; Congo Screening Study Group (2017). Determinants of cervical cancer screening accuracy for visual inspection with acetic acid (VIA) and Lugol's iodine (VILI) performed by nurse and physician. *PLoS One*. 12(1):e0170631. doi:10.1371/journal.pone.0170631 PMID:28107486

Sahasrabuddhe VV, Bhosale RA, Kavatkar AN, Nagwanshi CA, Joshi SN, Jenkins CA, et al. (2012). Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among HIV-infected women in India. *Int J Cancer*. 130(1):234–40. doi:10.1002/ijc.25971 PMID:21387289

Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, et al. (2007). Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised

trial. *Lancet*. 370(9585):398–406. doi:10.1016/S0140-6736(07)61195-7 PMID:17679017

Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. (2009). HPV screening for cervical cancer in rural India. *N Engl J Med*. 360(14):1385–94. doi:10.1056/NEJMoa0808516 PMID:19339719

Sankaranarayanan R, Nessa A, Esmy PO, Dangou JM (2012). Visual inspection methods for cervical cancer prevention. *Best Pract Res Clin Obstet Gynaecol*. 26(2):221–32. doi:10.1016/j.bpobgyn.2011.08.003 PMID:22075441

Sankaranarayanan R, Shastri SS, Basu P, Mahé C, Mandal R, Amin G, et al. (2004). The role of low-level magnification in visual inspection with acetic acid for the early detection of cervical neoplasia. *Cancer Detect Prev*. 28(5):345–51. doi:10.1016/j.cdp.2004.04.004 PMID:15542259

Sankaranarayanan R, Wesley R, Somanathan T, Dhakad N, Shyamalakumary B, Amma NS, et al. (1998). Visual inspection of the uterine cervix after the application of acetic acid in the detection of cervical carcinoma and its precursors. *Cancer*. 83(10):2150–6. doi:10.1002/(SICI)1097-0142(19981115)83:10<2150::AID-CNCR13>3.0.CO;2-0 PMID:9827719

Sankaranarayanan R, Wesley RS, editors (2003). A practical manual on visual screening for cervical neoplasia (IARC Technical Publications, No. 41). Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/364.

Shastri SS, Dinshaw K, Amin G, Goswami S, Patil S, Chinoy R, et al. (2005). Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bull World Health Organ*. 83(3):186–94. PMID:15798842

Shastri SS, Mittra I, Mishra GA, Gupta S, Dikshit R, Singh S, et al. (2014). Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. *J Natl Cancer Inst*. 106(3):dju009. doi:10.1093/jnci/dju009 PMID:24563518

Vorsters A, Arbyn M, Baay M, Bosch X, de Sanjosé S, Hanley S, et al. (2017). Overcoming barriers in HPV vaccination and screening programs. *Papillomavirus Res*. 4:45–53. doi:10.1016/j.pvr.2017.07.001 PMID:29179869

Wentzensen N, Walker JL, Gold MA, Smith KM, Zuna RE, Mathews C, et al. (2015). Multiple biopsies and detection of cervical cancer precursors at colposcopy. *J Clin Oncol*. 33(1):83–9. doi:10.1200/JCO.2014.55.9948 PMID:25422481

WHO (2013a). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/94830https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/.

WHO (2013b). Monitoring national cervical cancer prevention and control programmes: quality control and quality assurance for visual inspection with acetic acid (VIA)-based programmes. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/79316.

WHO (2014). Comprehensive cervical cancer control: a guide to essential practice. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/144785.

WHO (2017). Training of health staff in VIA, HPV detection test and cryotherapy – trainees' handbook. New Delhi, India: World Health Organization Regional Office for South-East Asia. Available from: https://apps.who.int/iris/handle/10665/259001.

WHO (2019). WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/329299.

Xue Z, Novetsky AP, Einstein MH, Marcus JZ, Befano B, Guo P, et al. (2020). A demonstration of automated visual evaluation of cervical images taken with a smartphone camera. *Int J Cancer*. 147(9):2416–23. doi:10.1002/ijc.33029 PMID:32356305

Zhao FH, Lin MJ, Chen F, Hu SY, Zhang R, Belinson JL, et al.; Cervical Cancer Screening Group in China (2010). Performance of high-risk human papillomavirus DNA testing as a primary screen for cervical cancer: a pooled analysis of individual patient data from 17 population-based studies from China. *Lancet Oncol*. 11(12):1160–71. doi:10.1016/S1470-2045(10)70256-4 PMID:21075054

Zhao XL, Xu XQ, Duan XZ, Rezhake R, Hu SY, Wang Y, et al. (2020). Comparative performance evaluation of different HPV tests and triaging strategies using self-samples and feasibility assessment of thermal ablation in 'colposcopy and treat' approach: a population-based study in rural China. *Int J Cancer*. 147(5):1275–85. doi:10.1002/ijc.32881 PMID:31970767

4.3 Cytological methods

4.3.1 Technical descriptions

Cytology is an established method of primary screening that is used to identify preclinical lesions and prevent the development of invasive cancer (Morrison, 1992). The technique of cervical cytology was developed by Papanicolaou and Babeş in the 1920s and later improved by Papanicolaou (Swailes et al., 2019). In the 1960s, cervical cytology was adopted for cervical cancer screening and was introduced in some high-income countries. Since then, the primary aim of the Pap test has shifted from the detection of invasive cancer to the identification of precancerous lesions. The main method used in primary screening has changed from cytology to HPV testing, particularly in Australia, some European countries, and the USA (Cuschieri et al., 2018) (see Section 2.2). However, in some countries, cytology still has a significant role in primary screening and triage. To reduce unnecessary colposcopy, a triage step has been introduced after the detection of low-grade abnormalities (see Section 4.4.7). Although cytology is used for this purpose, HPV testing, p16/Ki-67 dual staining, and some molecular biomarkers have been adopted as alternative methods.

(a) Conventional cytology

The conventional cytology technique involves collecting exfoliated cells from the TZ and endocervical canal. The precursors of cervical squamous cell carcinoma (SCC) occur mainly in the transformation zone (Burghardt, 1970). Thus, endocervical and/or metaplastic cells from the transformation zone are necessary for the adequacy of the sample (Arbyn et al., 2008a). However, the absence of endocervical cells is not necessarily associated with a high risk of future cervical neoplasia (Mitchell, 2001; McCredie et al., 2008; Sultana et al., 2014).

The quality of the smear is an essential component of the cytological interpretation. If too few cells are taken, the sample will not be representative of cells from the cervix (National Institute for Health and Clinical Excellence, 2003) and will be classified as unsatisfactory, because it cannot be interpreted. Unsatisfactory samples prevent the microscopic evaluation. A cervical sample is usually taken by a health service provider, such as a gynaecologist, general physician, midwife, or trained nurse (McDonald et al., 2001; Ideström et al., 2007; Yabroff et al., 2009; Cooper & Saraiya, 2014). Training of health providers in smear collection to ensure that samples are of adequate quantity and quality plays a critical role in quality assurance (see Section 4.3.1f).

Ideally, cytological examinations should be performed about 2 weeks after the first day of the previous menstrual period (IARC, 2005; Arbyn et al., 2008a). Sexual intercourse within 24 hours and use of intravaginal estrogen products should be avoided before cytological examinations. After childbirth, it is difficult to take adequate cervical samples for interpretation until 8 weeks postpartum.

The use of an appropriate collection device is essential in helping to reduce the proportion of unsatisfactory smears. Various instruments are used for taking smears, including cotton swabs, wooden spatulas, plastic spatulas, cytobrushes, and cervical brooms (Cervex-Brush). A study in Japan reported that before the introduction of the Bethesda system, more than 10% of smears collected using cotton swabs were reported as unsatisfactory (Hosono et al., 2018). Martin-Hirsch et al. (2000) compared collection devices for obtaining cytological samples in a systematic review of randomized and non-randomized comparative studies. The cervical broom is a commonly used device, and it was found that smears taken with it are adequate and comparable to those taken with a spatula (Peto odds ratio, 1.08; 95% CI, 0.97–1.21). However, a spatula

with an attached cytobrush performed better than the cervical broom alone (Peto odds ratio, 1.52; 95% CI, 1.15–2.01).

Cells collected for microscopic examination are applied to a glass slide for conventional cytology and commonly fixed using 95% ethyl alcohol covering the whole cellular area of the slide (Arbyn et al., 2008a). Cell fixation is performed within a few seconds of specimen collection to prevent air-drying, which obscures cellular detail and hinders interpretation (Somrak et al., 1990). The conventional Pap test technique may sometimes result in unsatisfactory smears, which are difficult to interpret because of uneven cell distribution, overlapping cells, blood, or inflammation (Taylor et al., 2006; Ronco et al., 2006, 2007).

(b)   Liquid-based cytology

Liquid-based cytology (LBC) is a more recent technique for transferring the cellular material to the microscope slide (Arbyn et al., 2008a). The brush with the sample is rinsed into a vial with preservative fluid and then transported to the laboratory (Siebers et al., 2009). This results in cells that better represent the sample being transferred to the glass slide when compared with conventional cytology (Payne et al., 2000). An LBC preparation more consistently results in a monolayer and reduces the proportion of unsatisfactory slides by avoiding transfer of blood and mucus. The subsequent process for staining and microscopic assessment of a slide is similar to that used in conventional cytology. However, LBC enables improved fixation, which leads to more consistent staining; this contributes to improved quality and readability. Training in the preparation technique and in the interpretation of LBC-specific slides is required for medical staff and cytologists (Payne et al., 2000). A major advantage of LBC over conventional cytology is that residual cell material can be used for additional testing, including testing for HPV and molecular biomarkers. A disadvantage is the need

for specific equipment for LBC and the substantial increase in unit costs (Payne et al., 2000; Taylor et al., 2006; Arbyn et al., 2008a). Several materials for LBC are available as commercial systems, for example the ThinPrep Imaging System and the BD FocalPoint GS Imaging System (SurePath).

LBC has been reported to reduce the rate of unsatisfactory samples in some population-based programmes. In a population-based cervical cancer screening programme in the Netherlands, unsatisfactory rates were reported to be 0.89% for conventional cytology and 0.13% for LBC (Beerman et al., 2009). In England, a pilot study reported that the rate of unsatisfactory samples decreased from 9.1% with Pap smears to 1.6% with LBC; in Scotland, the decrease was from 13.6% to 1.9% (National Institute for Health and Clinical Excellence, 2003; Williams, 2006). However, recent reports from Asian countries have suggested that there was no significant difference between LBC and conventional cytology in the rate of unsatisfactory smears (Kituncharoen et al., 2015; Hosono et al., 2018). A low rate of unsatisfactory smears in conventional cytology may reflect a good quality assurance system (Schneider et al., 2000; Petry et al., 2003; Klug et al., 2013). In 9 of 11 RCTs, the rate of unsatisfactory cytology was halved using LBC compared with conventional cytology (see Section 4.3.3, Table 4.15).

When LBC is used, the samples taken can be used for additional investigations, such as HPV testing, without needing to recall the woman (Cox, 2009; Albrow et al., 2012). LBC has been used with HPV testing as a primary screening method or for triage of HPV-positive women. When co-testing was used, the detection rate of CIN2+ increased, but rates of referral for colposcopy doubled compared with LBC alone (Kitchener et al., 2009). When LBC was used to triage HPV-positive women, the detection rate was increased and there was also an increase in the rate of colposcopy referrals compared

with LBC screening followed by HPV triage of abnormal LBC (Ogilvie et al., 2017).

A major problem with LBC is the high cost of the equipment and consumables required for the established commercial LBC methods; this is a considerable barrier to its use in resource-constrained settings (Arbyn et al., 2008a; Gupta et al., 2017; Pankaj et al., 2018).

A manual method for LBC was developed by Maksem et al. (2001). Nandini et al. (2012) reported that the concordance between manual LBC and histopathology was improved compared with CC. Because manual LBC is less expensive than commercial LBC systems, it might be a good alternative in low-resource settings.

(c) Computer-assisted cytology

Computer-assisted screening systems for both conventional cytology and LBC have been available since the early 2000s; these enable rapid interpretation of slides, which means that fewer professionals are needed (Thrall, 2019). In particular, some of these systems were developed to rapidly identify slides with normal cytology results that do not require further manual review.

The sensitivity and specificity of the PAPNET system, the first computer-assisted system for conventional cytology, was reported to be equal to that of conventional cervical screening (Doornewaard et al., 1999; Duggan, 2000). In population-based screening in the Netherlands, Kok & Boon (1996) reported that the diagnosis of HSIL and invasive cancer was higher for PAPNET than for conventional cytology. A study in Finland was the first RCT to evaluate the efficacy of automated screening using PAPNET (Nieminen et al., 2003, 2007; Anttila et al., 2011). More cases of LSIL were detected by screening with computer-assisted than with conventional cytology (RR, 1.08; 95% CI, 1.01–1.15), and significantly more cases of CIN1+ were detected with computer-assisted cytology (RR, 1.11; 95% CI, 1.02–1.21) (Nieminen et al., 2007). However, after 6.3 years of follow-up, no difference was found

in the risk of cervical cancer (RR, 1.00; 95% CI, 0.76–1.29) or of death from cervical cancer (RR, 1.11; 95% CI, 0.62–1.92) (Anttila et al., 2011).

For two more recently developed systems, ThinPrep and FocalPoint/SurePath, sensitivity and specificity were assessed by comparing the results with manual diagnosis by experts of the same slides (Biscotti et al., 2005; Wilbur et al., 2009). The sensitivities and specificities were nearly equivalent even when the test threshold was changed (Table 4.6).

A study in Australia evaluated the detection and unsatisfactory rate of the ThinPrep imager on the basis of 55 164 split-sample pairs (Davey et al., 2007). There were fewer unsatisfactory slides with the ThinPrep imager than with conventional cytology. LBC with the ThinPrep imager detected 1.3 more cases of high-grade lesions per 1000 women screened than conventional cytology.

The Manual Assessment Versus Automated Reading In Cytology (MAVARIC) trial was conducted to compare two automated systems (ThinPrep and FocalPoint/SurePath) with manual screening for the introduction of national programmes in England (Kitchener et al., 2011). The relative sensitivities of automated systems for CIN2+ compared with manual screening were nearly equal (ThinPrep relative sensitivity, 0.92; 95% CI, 0.87–0.98; FocalPoint relative sensitivity, 0.90; 95% CI, 0.85–0.96).

In an RCT in Germany, manual and automated LBC systems were compared (Klug et al., 2013). The relative sensitivity with LSIL as the threshold was 3.17 (95% CI, 1.94–5.19) for CIN2+ detection and 3.38 (95% CI, 3.38–6.21) for CIN3+ detection. Although the automated LBC system detected more CIN, the PPVs were equivalent. The relative PPV was 1.07 (95% CI, 0.75–1.53) for CIN2+ detection and 1.09 (95% CI, 0.66–1.80) for CIN3+ detection. In Denmark, Rebolj et al. (2015) assessed CIN detection rates and false-positive rates of LBC and computer-assisted reading based on routine screening data in a real-world

Table 4.6 Systematic reviews of studies of test performance of manual diagnosis compared with automated screening[a]

Test threshold	Manual		Automated (ThinPrep)		Reference
	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	
ASC-US	75.6 (72.2–78.8)	97.6 (97.2–97.9)	82.0 (78.8–84.8)	97.8 (97.2–97.9)	Biscotti et al. (2005)
LSIL	79.7 (75.3–83.7)	99.0 (98.8–99.2)	79.2 (74.7–83.2)	99.1 (98.9–99.3)	Biscotti et al. (2005)
HSIL	74.1 (66.0–81.2)	99.4 (99.2–99.6)	79.9 (72.2–86.2)	99.6 (99.5–99.7)	Biscotti et al. (2005)
	Manual		Automated (FocalPoint)		
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	
ASC-US	82.6	82.7	81.1	84.5	Wilbur et al. (2009)
LSIL	76.4	90.6	86.1	88.7	Wilbur et al. (2009)
HSIL	65.7	97.7	85.3	95.1	Wilbur et al. (2009)

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

[a] Reference standards in both studies were defined as the diagnosis of cytology carried out by experts in each study.

setting. For women aged 23–29 years with an atypical squamous cells of undetermined significance (ASC-US) threshold, the FocalPoint/SurePath system significantly increased the detection of CIN3+ (relative sensitivity, 1.85; 95% CI, 1.55–2.21) compared with manually read conventional cytology, but the increase was not significant using ThinPrep (relative sensitivity, 1.11; 95% CI, 0.88–1.39). The detection rate and false-positive rate of automated LBC depended upon brand and age group.

(d) The Bethesda system

The Bethesda system (TBS) is widely used for reporting cervical cytological diagnoses, but the Pap and WHO systems are also used in some areas. The relationship between the systems currently in use is shown in Fig. 1.17 (see also Section 1.2.3). In TBS 2001, the results of smears are assessed for specimen adequacy and divided into three categories: negative for intraepithelial lesion or malignancy (NILM), epithelial cell abnormalities (with either squamous cells or glandular cells), and others. Squamous cell abnormalities are classified as follows: ASC-US; atypical squamous cells, cannot exclude HSIL

(ASC-H); LSIL; HSIL; and SCC. Of women with atypical squamous cells (ASC), 10–20% have underlying CIN2 or CIN3 and 0.1% have invasive cancer (Solomon et al., 2001). Specific glandular cell abnormalities are classified as follows: atypical glandular cells; atypical glandular cells, favour neoplastic; endocervical adenocarcinoma in situ; and adenocarcinoma.

Advances in the understanding of HPV biology and histological advances were reflected in a revision of TBS in 2014 (Nayar & Wilbur, 2015; Table 4.7). Most of the changes were small, but two major changes were made. In TBS 2014, the cut-off age for reporting benign endometrial cells was changed from 40 years to 45 years. Follow-up studies had reported that the incidence of endometrial carcinoma differed between women in their forties and in their fifties (Weiss et al., 2016; Colletti et al., 2017; Grada et al., 2017; Hinson et al., 2019). In addition, TBS 2014 added chapters covering adjunctive testing, computer-assisted interpretation, education, and risk assessment in cervical cancer (Massad et al., 2013).

Table 4.7 The 2014 Bethesda System for Reporting Cervical Cytology

SPECIMEN TYPE
Indicate conventional smear (Pap smear) vs liquid-based preparation vs other
SPECIMEN ADEQUACY
• Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality indicators, e.g. partially obscuring blood, inflammation, etc.)
• Unsatisfactory for evaluation (specify reason)
o Specimen rejected/not processed (specify reason)
o Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality (specify reason)
GENERAL CATEGORIZATION (OPTIONAL)
• Negative for intraepithelial lesion or malignancy
• Other: see Interpretation/Result (e.g. endometrial cells in a woman aged ≥ 45 years)
• Epithelial cell abnormality: see Interpretation/Result (specify squamous or glandular, as appropriate)
INTERPRETATION/RESULT
Negative for intraepithelial lesion or malignancy
When there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report – whether or not there are organisms or other non-neoplastic findings
Non-neoplastic findings (optional to report)
• Non-neoplastic cellular variations
o Squamous metaplasia
o Keratotic changes
o Tubal metaplasia
o Atrophy
o Pregnancy-associated changes
• Reactive cellular changes associated with:
o Inflammation (includes typical repair)
– Lymphocytic (follicular) cervicitis
o Radiation
o Intrauterine contraceptive device (IUD)
• Glandular cells status post-hysterectomy
Organisms
• *Trichomonas vaginalis*
• Fungal organisms morphologically consistent with *Candida* spp.
• Shift in flora suggestive of bacterial vaginosis
• Bacteria morphologically consistent with *Actinomyces* spp.
• Cellular changes consistent with herpes simplex virus
• Cellular changes consistent with cytomegalovirus
Other
• Endometrial cells (in a woman aged ≥ 45 years)
(Specify if negative for squamous intraepithelial lesion)
Epithelial cell abnormalities
Squamous cell
• Atypical squamous cells
o Of undetermined significance
o Cannot exclude HSIL
• LSIL (encompassing: HPV/mild dysplasia/CIN1)
• HSIL (encompassing: moderate and severe dysplasia, CIS; CIN2 and CIN3)
o With features suspicious for invasion (if invasion is suspected)
• Squamous cell carcinoma

Table 4.7 (continued)

Glandular cell
• Atypical
o Endocervical cells (NOS or specify in comments)
o Endometrial cells (NOS or specify in comments)
o Glandular cells (NOS or specify in comments)
• Atypical
o Endocervical cells, favour neoplastic
o Glandular cells, favour neoplastic
• Endocervical adenocarcinoma in situ
• Adenocarcinoma
o Endocervical
o Endometrial
o Extrauterine
o NOS
Other malignant neoplasms (specify)
ADJUNCTIVE TESTING
Provide a brief description of the test method(s) and report the result so that it is easily understood by the clinician
COMPUTER-ASSISTED INTERPRETATION OF CERVICAL CYTOLOGY
If case examined by an automated device, specify device and result
EDUCATIONAL NOTES AND COMMENTS APPENDED TO CYTOLOGY REPORTS (optional)
Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included).

CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NOS, not otherwise specified.

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Although the scientific community has made considerable efforts to standardize the criteria for cervical cytology classification, the interpretation of cytology results in substantial variability. For example, in a multicentre RCT designed to evaluate the interpretation of mildly abnormal cytology findings, the reproducibility of monolayer cytological interpretations was moderate (kappa value, 0.46; 95% CI, 0.44–0.48) (Stoler et al., 2001). The disagreement was particularly strong for the ASC-US category, where the concordance was only 42.3%. Studies in Europe also reported disagreement in the ASC-US category (kappa value, 0.10; 95% CI, 0.07–0.13), and the results could not be improved after discussion (kappa value, 0.12; 95% CI, 0.09–0.15) (Ronco et al., 2003). In the first Bethesda Interobserver Reproducibility Study (BIRST-1), 77 images were interpreted by 216 cytotechnologists and 185 pathologists, all of whom were highly experienced, but agreement was obtained for only 67.9% of NILM, 54.1% of LSIL, 22.4% of ASC-H, and 39.9% of ASC-US (Sherman et al., 2007). In the BIRST-2 study for TBS 2014, 518 international participants interpreted 84 digital images (Kurtycz et al., 2017). The overall agreement was 62.8%, which was higher than that in the BIRST-1 study (55.3%). The best agreement was found for NILM (73.4%) and LSIL (86.3%); other results were as follows: 61.7% for ASC-US and 59.5% for HSIL. In a recent study in Brazil, 6536 examinations were reviewed and it was found that kappa values increased from 0.84 to 0.94 (de Morais et al., 2020).

(e) p16/Ki-67 dual staining

The p16^{INK4a} (p16) protein has been widely used in immunocytochemical staining as a biomarker for transforming HPV infection (von Knebel Doeberitz, 2002). The overexpression of p16 in cervical dysplasia is associated with the expression of the E7 oncoprotein of carcinogenic HPV types and can be a surrogate marker of the E7-mediated inactivation of the tumour-suppressor function of the retinoblastoma protein (Schmidt et al., 2011). p16 overexpression is directly connected to cellular transformation by HPV, because E7 expression is required to maintain the phenotype in HPV-associated cancers (von Knebel Doeberitz et al., 1992). p16 overexpression is found in most cervical precancerous lesions and cancers, but it is rarely observed in normal tissue (Klaes et al., 2001).

The expression of the proliferation marker Ki-67 within the same cervical epithelial cell can be used as a surrogate marker of cell cycle deregulation mediated by transforming HPV infection. Although p16/Ki-67 dual staining is independent of morphological interpretation, the interpretation of positive results is operator-independent, not automated. When slides show cervical epithelial cells with brown cytoplasmic p16 immunostaining and red nuclear Ki-67 immunostaining, they could be interpreted as a positive result (Petry et al., 2011). The p16 positivity rate is determined by the distribution of the staining into the cytoplasm or the nucleus and the number of cells that display an overexpression of biomarkers (Tsoumpou et al., 2009). Although the cut-off value varied across the studies, the classification proposed by Klaes et al. (2001) was commonly used. The sensitivity of p16/Ki-67 dual staining using a two-cell cut-off value was nearly equal to that of cytology (82.8% vs 83.8%), but the specificity was higher (62.8% vs 48.7%) (Wentzensen et al., 2005). Although Tsoumpou et al. (2009) reported that the reproducibility of p16 immunostaining is limited because there are insufficient standards for interpretation, recent studies have reported good reproducibility, with kappa values from 0.6 to 0.7 (Stoler et al., 2001; Confortini et al., 2007; Allia et al., 2015; Benevolo et al., 2017). There was no difference in kappa values between experts and non-experts for the interpretation of slides from HPV-positive women (Allia et al., 2015).

p16/Ki-67 dual staining is used for cervical cancer screening, with its use divided into three patterns: primary screening, triage of abnormal cytology, and triage of HPV-positive results. The Primary ASC-US and LSIL Marker (PALM) study was an international collaborative study to evaluate the sensitivity and specificity of p16/Ki-67 dual-stain cytology for primary screening in European countries (Ikenberg et al., 2013). The use of p16/Ki-67 dual staining for primary screening is no longer considered to be an option, because there is a stronger rationale for its use for triage of borderline cytology (ASC-US or LSIL) (Peeters et al., 2019) and, more importantly, of HPV-positive women (Wentzensen et al., 2016; Cuschieri et al., 2018).

In a systematic review, Peeters et al. (2019) compared p16/Ki-67 dual staining with high-risk HPV (hrHPV) testing for triage of ASC-US. The meta-analysis confirmed that p16/Ki-67 dual staining was less sensitive for detection of CIN2+ compared with hrHPV testing (84% vs 93%) but more specific for triage of ASC-US (77% vs 45%). Similar results were obtained when p16 staining was used for triage of ASC-US or when the abnormal cytology threshold was changed to ASC-H (Roelens et al., 2012; Xu et al., 2016).

The sensitivity and specificity of p16/Ki-67 dual staining for women with HPV-positive results were compared with those of cytology, HPV16/18 genotyping, and these methods in combination (Table 4.8). Most studies reported that the sensitivity of p16/Ki-67 dual staining for the detection of CIN2+ was 80–90%. Compared with cytology, the sensitivity of p16/Ki-67 dual staining for the detection of CIN2+ was higher,

Table 4.8 Comparison of performance of p16/Ki-67 dual staining, cytology, and HPV16/18 genotyping for triage of women with HPV-positive results

Reference Country	Outcome: CIN2+						Outcome: CIN3+					
	Sensitivity (%) (95% CI)			Specificity (%) (95% CI)			Sensitivity (%) (95% CI)			Specificity (%) (95% CI)		
	p16/Ki-67 dual staining	Cytology (ASC-US+)	HPV16/18 genotyping	p16/Ki-67 dual staining	Cytology (ASC-US+)	HPV16/18 genotyping	p16/Ki-67 dual staining	Cytology (ASC-US+)	HPV16/18 genotyping	p16/Ki-67 dual staining	Cytology (ASC-US+)	HPV16/18 genotyping
Petry et al. (2011) Germany	91.9 (78.1–98.3)	NA	NA	82.1 (72.9–89.2)	NA	NA	NA	NA	NA	NA	NA	NA
Wentzensen et al. (2012) USA	85.5 (77.8–90.9)	NA	47.6 (38.6–56.7)	59.4 (53.3–65.1)	NA	80.8 (75.5–85.2)	90.6 (73.8–97.5)	NA	75.0 (71.3–80.3)	48.6 (43.5–53.9)	NA	76.1 (71.3–80.3)
Wentzensen et al. (2015) USA	83.4 (77.1–88.6)	76.6 (69.6–82.6)	NA	58.9 (56.2–61.6)	49.6 (46.9–52.3)	NA	86.9 (78.6–92.8)	83.8 (75.1–90.5)	NA	56.9 (54.2–59.5)	48.7 (46.1–51.4)	NA
Gustinucci et al. (2016) Italy	87.6 (75.7~93.6)	77.6 (65.3–86.7)	47.0 (34.0–58.9)	74.9 (69.0–79.0)	72.5 (67.2–77.2)	77.9 (72.8–82.0)	92.3 (74.9–99.1)	96.3 (81.0–99.9)	63.0 (42.4–80.6)	NA	NA	NA
Wright et al. (2017) USA	70.3 (65.3–74.9)	51.8 (46.5–58.3)	NA	75.6 (74.0–77.1)	76.1 (74.6–77.7)	NA	74.9 (69.0–75.7)	51.9 (45.4–58.3)	NA	74.1 (72.5–75.7)	75.0 (73.5–76.5)	NA
Stanczuk et al. (2017) United Kingdom	85.0 (73.4–92.9)	68.3 (55.0–79.7)	61.7 (48.2–73.9)	76.7 (71.1–81.8)	89.1 (84.7–92.7)	70.5 (64.6–76.0)	NA	NA	NA	NA	NA	NA
Wentzensen et al. (2019) USA	88.6 (84.5–92.6)	84.3 (79.7–89.0)	NA	53.1 (51.3–54.9)	42.9 (41.1–44.6)	NA	82.8 (79.4–86.2)	81.1 (77.6–84.7)	NA	55.7 (53.9–57.6)	44.6 (42.9–46.5)	NA
Stoler et al. (2020) USA	NA	NA	NA	NA	NA	NA	86.0	77.2	59.1	60.1	61.6	76.5
Hu et al. (2020) China	63.5 (54.4–71.9)	61.9 (52.8–70.4)	61.9 (52.8–70.4)	85.3 (82.5–87.8)	80.0 (76.9–82.9)	72.4 (68.9–75.6)	64.7 (55.2–73.3)	62.9 (53.5–71.7)	62.9 (53.5–71.7)	84.8 (82.0–87.3)	79.6 (76.5–82.5)	72.1 (68.6–75.3)
Jiang et al. (2020) China	75.0 (50.9–91.3)	NA	NA	50.3 (41.9–58.8)	NA	NA	83.3 (35.9–99.6)	NA	NA	42.7 (34.8–50.8)	NA	NA

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; NA, not available.

Table 4.9 Comparison of guidelines for quality assurance for cytology

Component	Guideline (year published)		
	European Commission (2008)[a]	United Kingdom (2019–2020)[b]	Australia (2018–2019)[c]
Training		✓	✓
Sample collection	✓	✓	✓
Organization (staff, workload)	✓	✓	✓
Material requirement	✓	✓	✓
Quality management	✓	✓	✓
Terminology	✓	✓	✓
Management of abnormal cytology	✓	✓	✓
Follow-up	✓	✓	✓
Laboratory performance indicators	✓	✓	✓
Quality improvement (audit)		✓	✓

[a] Arbyn et al. (2008a).
[b] Public Health England (2019a, b, 2020).
[c] National Pathology Accreditation Advisory Council (2019).
Table compiled by the Working Group.

but the specificity ranged from 50% to 85%; the sensitivity for the detection of CIN3+ was higher, and the specificity was nearly equal. In contrast, the sensitivity of p16/Ki-67 dual staining for the detection of CIN2+ or CIN3+ was always higher than that of HPV16/18 genotyping, but the specificity was lower. Recent studies have reported that combining HPV16/18 genotyping with p16/Ki-67 dual staining increased the sensitivity, with a slight decrease in specificity (Wright et al., 2017; Wentzensen et al., 2019). In Section 4.4.7, the sensitivity and specificity of this combined method for triage of HPV-positive women are compared with those of five other triage methods.

(f) Quality assurance for cytology

Cytological examination depends on the skill and experience of the individual; the interpretation of cervical samples under the microscope is particularly subjective (Arbyn et al., 2008a). The standardization of cytological procedures should always be considered to ensure they are of good quality. Quality assurance should be included in all programmes related to cervical cancer screening, and laboratory management has an

important role in quality improvement (Branca & Longatto-Filho, 2015). Continued attention to quality improvement is recommended to ensure that women have access to high-quality screening. Organizational approaches for laboratories include components that address smear-taking, education of both cytotechnologists and cytopathologists, establishment of laboratory quality assurance programmes, management of abnormal cytology, and protocols for follow-up (Farnsworth, 2016). In addition to the European guidelines that established the basic concepts of quality assurance (Arbyn et al., 2008a), guidelines for laboratory quality assurance published in Australia and the United Kingdom also included basic components needed for management and quality improvement (Public Health England, 2019a, b, 2020; National Pathology Accreditation Advisory Council, 2019; Cancer Council Australia Cervical Cancer Screening Guidelines Working Party, 2020) (Table 4.9).

Training for cytotechnologists and cytopathologists is critical for the quality improvement of cytology. For quality assurance of cervical screening, professional accreditation has been

provided on the basis of educational programmes for cytotechnologists. The European guidelines for quality assurance describe the different educational programmes in European countries (Arbyn et al., 2008a). The Australian and United Kingdom guidelines clarify their educational policy and required accreditations for cytotechnologists (National Pathology Accreditation Advisory Council, 2019; Cancer Council Australia Cervical Cancer Screening Guidelines Working Party, 2020; Public Health England, 2020). The National Health Service (NHS) Cervical Screening Programme has also provided educational programmes for smear-takers including general physicians, nurses and midwives (Public Health England, 2016). Continuous training is also required to maintain the quality of interpretation and administration. To harmonize training and develop a quality standard for cervical cancer screening, the Transnational Training Programme in Cervical Cytology (CYTOTRAIN) has produced training materials for cytotechnologists and cytopathologists in Europe (Herbert et al., 2014).

To ensure the accuracy of slide interpretation, cytology laboratories must control the workload of cytotechnologists to help avoid mistakes caused by fatigue or haste (CDC, 1997). Tarkkanen et al. (2003) reported that the annual workload varied among laboratories in Helsinki and the daily average was 30–40 smears. The detection of abnormalities is associated with time spent screening; cytotechnologists with a restricted workload perform better (Renshaw & Elsheikh, 2013). In Australia, the maximum workload for any person involved in primary examination of LBC is 70 slides per day and the hourly workload must not exceed 10 slides (National Pathology Accreditation Advisory Council, 2019). In European countries, the workload limits vary from 25 to 80 slides per hour (Mody et al., 2000). In the USA, federal regulations require workloads to be less than 100 slides per 24 hours (College of American Pathologists,

2014). The American Society of Cytopathology has published quality assurance recommendations for automated screening, including recommendations about productivity and workloads for cytotechnologists (Elsheikh et al., 2013).

Laboratory performance standards for reporting cervical cytology have been established and commonly include rates of unsatisfactory smears, rates of detection of abnormalities, PPVs, and false-negative rates (College of American Pathologists, 2014; National Pathology Accreditation Advisory Council, 2019; Public Health England, 2019a). In the United Kingdom, external quality assessment is defined to assess the performance of cytopathology laboratories and to improve the preparation of LBC slides (Public Health England, 2016).

Quality improvement is an integral component of the management process, and it makes the programmes safe and effective. An audit is the inspection of the quality assurance system to ensure compliance with standards (Branca & Longatto-Filho, 2015). In Australia, a summary of each laboratory's performance standards is submitted annually to the Royal College of Pathologists Quality Assurance Program for collation (Farnsworth, 2016). Laboratories are inspected at least every 3 years and are required to meet these performance measures to claim financial reimbursement. In the United Kingdom, an annual audit programme is carried out to ensure continuous improvement (Public Health England, 2019a).

Some countries have a cytology registry database for quality control and assessment at a national level. In the Netherlands, such a system, the Dutch Network and National Database for Pathology (PALGA), has been in place since 1990 (van Ballegooijen & Hermens, 2000; Casparie et al., 2007). The system has information on all the cytology and pathology results that the laboratories have recorded. In Australia, the state-based Pap test registries collect individual women's cervical cytology and pathology results

from laboratories (Farnsworth, 2016). The system enables direct follow-up in women who receive abnormal results. In Europe, countries collaborate and compare performance indicators of the programmes (Ronco et al., 2009). The low reproducibility of cytology interpretation can be seen when the proportions of abnormal tests, their distribution by grade, and the PPVs are compared among different population-based screening programmes operating in areas with a homogeneous epidemiology of cervical cancer and screening coverage.

Quality assurance systems differ in resource-constrained settings. Cytology screening requires trained personnel and adequate quality control, and quality assurance is frequently insufficient in resource-constrained settings (Gupta et al., 2017). In southern Thailand, Chichareon et al. (2005) found that abnormal cytology detection rates varied from 0.57% to 3.05%. In these areas, pathology laboratories and pathologists were insufficient in number, they underperformed, and the pathologists' roles were not specialized in hospital laboratories. High rates of unsatisfactory samples were reported in conventional cytology (52.3%) and also when LBC was used (47.5%) (Phaliwong et al., 2018). The insufficient follow-up of abnormal smears is also a serious problem. In Thailand, even in the university hospital, 56.1% of women with ASC-US results had colposcopy and 19% could not be followed up (Chichareon & Tocharoenvanich, 2002). Gage et al. (2003) reported a similar experience in Peru, where only 25% of 183 women with an abnormal smear received follow-up. Although cytology is a standardized screening method and the cost is relatively low, the absence of quality control is a major concern.

4.3.2 Beneficial effects of screening using conventional cytology

The 2005 *IARC Handbooks* review evaluated seven cohort studies and 20 case–control studies from multiple countries to review the efficacy of cytology screening in preventing cervical cancer (IARC, 2005). The studies produced consistent evidence of a benefit of cytology-based screening in reducing cervical cancer incidence, which was consistent with the accompanying comprehensive review of ecological trend data in cervical cancer incidence in multiple countries after the introduction of screening. National-level long-term ecological trend data published since the 2005 *IARC Handbook* from multiple countries and world regions continue to support the population-level effectiveness of cytology-based cervical screening (Vaccarella et al., 2013). This is supported by studies in, for example, Brazil (Reis et al., 2020), Canada (Dickinson et al., 2012), Chile (Sepúlveda & Prado, 2005; Pilleron et al., 2020), Europe (Bray et al., 2005; Mendes et al., 2018), the Nordic countries (Vaccarella et al., 2014; Pedersen et al., 2018), the Republic of Korea (Park et al., 2015), Thailand (Sriplung et al., 2014; Virani et al., 2018), Uruguay (Garau et al., 2019), and the USA (Yang et al., 2018). The 2005 *IARC Handbook* noted that the magnitude of the benefit (reduction in disease through screening) was highly variable. The review concluded that the variation in the size of the reduction in risk of cervical cancer through screening was caused largely by variations in the quality of cytology (which will affect its sensitivity) and in programme organization, rather than by measurement error.

The studies published since the 2005 *IARC Handbook* (IARC, 2005) are described and assessed here.

(a)   Randomized controlled trials

Only one RCT comparing cytology screening with control conditions (health awareness raising of symptoms and the availability of screening) using incidence and mortality as outcomes has been published (Sankaranarayanan et al., 2005, 2009) (Table 4.10 and Table 4.11). This cluster-randomized trial compared the impact of a single round of screening in four groups (13 clusters per group) – VIA, cytology, HPV testing, and control – in 52 villages in Osmanabad District in Maharashtra state, India. The estimated baseline cervical cancer incidence rate was high, at 20.0 per 100 000 women, with a largely unscreened high-risk population. The study included 131 746 women aged 30–59 years. Of 32 058 women in the cytology group, 25 549 (79.7%) were screened and 1787 (7.0%) had positive results. The PPV for detecting CIN2/3 was 19.3%. Of the 476 women diagnosed with CIN1, 214 were treated (45.0%), and of the 262 women diagnosed with CIN2/3, 234 (89.3%) were treated. During the 8-year follow-up period, cervical cancer developed in 22 of 23 762 women who had negative results on cytological testing (Sankaranarayanan et al., 2009). The diagnosed incidence of cervical cancer in the cytology group was higher than, although not statistically significantly different from, that in the control group (60.7 per 100 000 person-years vs 47.6 per 100 000 person-years; hazard ratio [HR], 1.34; 95% CI, 0.99–1.82). More advanced-stage cancers were diagnosed in the control group than in the cytology group, although this was not statistically significantly different (stage 2 or higher, 23.2 per 100 000 person-years vs 33.1 per 100 000 person-years; HR, 0.75; 95% CI, 0.51–1.10). Mortality from cervical cancer was lower, but not significantly lower, in the cytology group than in the control group (21.5 per 100 000 person-years vs 25.8 per 100 000 person-years; HR, 0.89; 95% CI, 0.62–1.27). [The Working Group noted that the main limitations of the study were that women in the control group were slightly older (mean age, 40 years vs 39 years) (which was adjusted for in the analysis), that screening after health awareness raising in the control group may have minimized the observed impact of screening, and in relation to cytology that a single round was conducted, when it is well established that cytology screening is optimally performed at regular intervals. These results confirmed that even one Pap test can have an impact on incidence of advanced cancers and mortality, but will increase incidence through earlier detection in a medium time period.]

(b)   Reviews and meta-analyses

In 2007, the International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC, 2007) published an analysis of individual-level data collated from 12 observational studies (one cohort study and 11 case–control studies) to analyse risk factors for cervical cancer by type and included history of screening with cytology in the analysis. The analysis included 8097 women with SCC, 1374 women with adenocarcinoma, and 26 445 control women. The women were aged 16–89 years, had not had a hysterectomy, and had had at least one sexual partner. In studies where it was not clear that diagnostic smears had been excluded, only screens 12 months before diagnosis were included. The analysis found that having a past Pap test was associated with a reduced risk of cervical cancer for both SCC (RR, 0.46; 95% CI, 0.42–0.50) and adenocarcinoma (RR, 0.68; 95% CI, 0.56–0.82).

The systematic review and meta-analysis of Peirson et al. (2013) assessed observational cervical screening studies with incidence and mortality as outcomes against unscreened women for the review period of 1995–2012 and published in English or French. The review identified the above-mentioned RCT of Sankaranarayanan et al. (2009) and two cohort studies, one of which was included in the 2005 *IARC Handbooks* review of cytology screening assessing screening

Table 4.10 Basic characteristics of the randomized trial on the efficacy of cervical cancer screening by conventional cytology

Reference	Location	No. of women (screened/ control group)	Accrual period for screening	Age at entry (years)	No. of examinations/ tests in screened/ control group	Incidence of all cervical cancer[a]		Cancer mortality[a]	
						Rate of cervical cancer per 100 000 person-years in screened/ control group	HR (95% CI)[b]	Rate of cervical cancer per 100 000 person-years in screened/ control group	HR (95% CI)[b]
[Sankaranarayanan et al. (2005, 2009)](#)	Cluster at village level, India	131 746 eligible women (32 058/31 488)	October 1999 to November 2003	30–59	25 549/1946	60.7/47.6	1.34 (0.99–1.82)	21.5/25.8	0.89 (0.62–1.27)

CI, confidence interval; HR, hazard ratio.

[a] Rates and hazard ratios have been adjusted for age.

[b] Hazard ratios are for the comparison between each intervention group and the control group.

Table 4.11 Results of the randomized trial on the efficacy of cervical cancer screening by conventional cytology

Reference Country	Age at enrolment or screening (years)	Mean duration of follow-up (years)	No. of subjects	Cancer mortality per 100 000 person-years (no. of cancer deaths) in screened/control group	RR (95% CI)
[Sankaranarayanan et al. (2009)](#) (see also [Sankaranarayanan et al., 2005](#)) India	30–59 Mean age: cytology group, 39; control group, 40	8	Cytology group, 32 058; control group, 31 488	21.5/25.8	0.89 (0.62–1.27)

CI, confidence interval; RR, relative risk.

interval (Herbert et al., 1996). The other cohort study (Rebolj et al., 2009) specifically assessed incidence and mortality in women after negative screens only, not all screened women. The findings of the review are described in the following sections, where included studies are detailed. Only one study overlaps between the meta-analysis of Peirson et al. (2013) and the ICESCC (2007) study: a case–control study of risk factors for cervical cancer from four Latin American countries, reported in two publications (Herrero et al., 1990, 1992).

(c)   Cohort studies

Table 4.12 summarizes the results of five cohort studies published since the 2005 *IARC Handbooks* review; two of them focused on older women (Wang et al., 2017; Pankakoski et al., 2019).

Over a period of 12 years, Odongua et al. (2007) followed up 475 398 women aged 30–95 years in the Republic of Korea; the women all had national health insurance and attended a biennial medical examination. Incidence of and death from cervical cancer were assessed using a combination of cancer registry, hospital, and death data records. Estimates were adjusted for age, body mass index, smoking status, alcohol consumption, menarche, and parity. Overall, 57% of women had ever had a Pap test. Compared with screened women with normal screening results, unscreened women had higher incidence of and mortality from cervical cancer (incidence: adjusted RR, 1.12; 95% CI, 1.00–1.25; mortality: adjusted RR, 2.00; 95% CI, 1.37–2.81). Women with abnormal screening results also had higher incidence and mortality than screen-negative women (incidence: adjusted RR, 2.81; 95% CI, 2.54–3.02; mortality: adjusted RR, 2.47; 95% CI, 1.74–3.53). [The Working Group noted that there is insufficient detail in the article to know whether, as seems likely from these findings, diagnostic smears from unscreened women with symptoms were included in the abnormal screening

results group. Most studies (see Table 4.12) exclude smears collected in the months before a diagnosis of cervical cancer as evidence of screening and classify women with only these tests as unscreened. If these women are considered as screened, the group of screened women with abnormal results will include unscreened women who develop cancer, biasing the effect of screening overall towards the null. An overall adjusted RR for all screened versus unscreened women is not provided in the study.]

Also in the Republic of Korea, Jun et al. (2009) used data from a national cohort study (the National Health Insurance Corporation Study), which included civil servants and private school employees and their dependents who had health insurance and who participated in at least one routine biennial medical examination between 1995 and 1996. In this study, 253 472 women aged 20 years or older were followed up until 2002 (baseline exclusions were women with previous hysterectomy or cancer; this was not a consent-based study and used routinely collected health information from the insurer). Biennial Pap screening and risk factor surveys were offered by local health services within the cohort, and 52% of women were screened at least once. In total, 241 415 Pap tests were collected, of which 110 were excluded (as diagnostic tests) because they were taken within 3 months of diagnosis of cancer, leaving 241 305 Pap tests. Screening frequency was defined as never, once, or twice or more. Cancer incidence data were taken from the Korean Central Cancer Registry and mortality data for 1995–2002 from the National Statistical Office. After adjustment for age, smoking status, and alcohol consumption, the results showed that women screened twice or more had lower rates of cervical cancer (RR, 0.29; 95% CI, 0.20–0.45), with no significant reduction in those screened only once compared with no screening (RR, 0.90; 95% CI, 0.68–1.18)). Two or more screens were protective against carcinoma in situ of the cervix and across age ranges from

Table 4.12 Cohort follow-up studies on the effectiveness of cervical cancer screening by conventional cytology

Reference Country	Cohort description: no. of women, screening period, source of screening data, and source of follow-up data	Established programme: year of start, screening age, screening interval	Accrual and follow-up periods Person-years	Cervical cancer or precancer end-point, and incidence or mortality age ranges	No. of cases or deaths	Cervical cancer incidence or mortality RR (95% CI)[a]	Adjustments	Comments
Odongua et al. (2007) Republic of Korea	475 398 women with national health insurance aged 30–95 yr who attended a biennial medical examination Screening data from insurance records Incidence and mortality data from national cancer registry, hospital records, and death data records from the National Statistical Office	1992, employees and dependents through national health insurance. In 2000, mandated Pap testing through National Health Insurance Law as part of National Cancer Screening Program	1992–2004 12 yr Person-yr not given	Cervical cancer incidence and mortality Age range at enrolment, 30–95 yr	2523 cases 209 deaths	Incidence: Compared with screened women with normal results (reference) Screened women with abnormal results: 2.81 (2.54–3.02) Unscreened women: 1.12 (1.00–1.25) Mortality: Compared with screened women with normal results (reference) Screened women with abnormal results: 2.47 (1.74–3.53) Unscreened women: 2.00 (1.37–2.81) [Unscreened reference group: Incidence: 0.89 (0.8–1.0) Mortality: 0.5 (0.36–0.73)] [Unscreened reference group: Incidence: 0.36 (0.33–0.39) Mortality: 0.40 (0.28–0.57)]	Age, BMI, smoking status, alcohol consumption, menarche, parity	Only compared unscreened women with screened women with normal results, not all screening. Not clear that diagnostic smears were excluded

Table 4.12   (continued)

Reference Country	Cohort description: no. of women, screening period, source of screening data, and source of follow-up data	Established programme: year of start, screening age, screening interval	Accrual and follow-up periods Person-years	Cervical cancer or precancer end-point, and incidence or mortality age ranges	No. of cases or deaths	Cervical cancer incidence or mortality RR (95% CI)[a]	Adjustments	Comments
Jun et al. (2009) Republic of Korea	253 472 women aged ≥ 20 yr Frequency of Pap testing was determined by the National Health Examination Database Cancer incidence was detected through the Korean Central Cancer Registry and mortality through the National Statistical Office	1988, employees and dependents through national health insurance. In 2000 mandated Pap testing through National Health Insurance Law; biennial cervical cancer screening during the follow-up period	1995–2002 Average follow-up time: 6.5 yr 1 657 130.4 person-yr	Incidence of invasive cervical cancer and CIS of the cervix Age ≥ 20 yr	248 cases of invasive cervical cancer 346 cases of CIS of the cervix	Compared with unscreened women (reference) Incidence of cervical cancer, ≥ 2 screens: 0.29 (0.20–0.45) Incidence of cervical cancer, 1 screen: 0.90 (0.68–1.18) Incidence of CIS of the cervix, ≥ 2 screens: 0.34 (0.25–0.46) Incidence of CIS of the cervix, 1 screen: 0.66 (0.51–0.85)	Age, smoking status, alcohol consumption	Women who were screened ≥ 2 times also had significantly lower rates of all cancers compared with women never screened [supporting the idea of a healthy participant effect]

Table 4.12   (continued)

Reference Country	Cohort description: no. of women, screening period, source of screening data, and source of follow-up data	Established programme: year of start, screening age, screening interval	Accrual and follow-up periods Person-years	Cervical cancer or precancer end-point, and incidence or mortality age ranges	No. of cases or deaths	Cervical cancer incidence or mortality RR (95% CI)[a]	Adjustments	Comments
Dugué et al. (2014) Denmark	1 156 671 women aged 23–51 yr on 1 January 1990 and alive on 31 December 1993 for the 1-round analysis, and 1 030 786 women aged 23–51 yr on 1 January 1990 and alive on 31 December 1997 for the 2-round analysis. Women with gaps in residence in Denmark were excluded In this period, all women were invited to 2 screening rounds, and cytology records were taken from the Danish Pathology Data Bank, National Health Service Register, and National Patient Register The women were followed up until 31 December 2010 (or death or emigration). Follow-up data were from the Danish Civil Registration System and Danish Cause of Death register using Danish unique personal identification numbers	1986, women 23–59 yr, personally invited every 3 yr (90% of women were covered by the guidelines in 1997). Since 2007, every 3 yr for women aged 23–49 yr and every 5 yr for those aged 50–65 yr	1998–2010 Person-yr not given	Mortality due to cervical cancer by screening status as never screened, irregularly screened (attended 1 of 2 rounds), compared with regularly screened (attended both rounds between 1990 and 1997)	No. of cervical cancer deaths: Never screened, 274 Irregularly screened, 152 Regularly screened, 237	Mortality HR compared with regularly screened (1.0) Never screened: 7.91 (6.62–9.46) Irregularly screened: 2.23 (1.81–2.73) [Unscreened reference group: Never screened: 0.13 (0.11–0.15) Irregularly screened: 0.45 (0.37–0.55)]	Adjusted for age by using attained age as time scale in Cox proportional hazards regression	Overall study findings in relation to all-cause mortality: unscreened women had 1.5–2× risk of dying compared with screened women, with a mortality gap maintained over 2 decades. This group also had almost 4× risk of death from other HPV-associated cancers Any cytology test included in screening [this will lead to underestimate of protection from screening]

Table 4.12   (continued)

Reference Country	Cohort description: no. of women, screening period, source of screening data, and source of follow-up data	Established programme: year of start, screening age, screening interval	Accrual and follow-up periods Person-years	Cervical cancer or precancer end-point, and incidence or mortality age ranges	No. of cases or deaths	Cervical cancer incidence or mortality RR (95% CI)[a]	Adjustments	Comments
Wang et al. (2017) Sweden	569 132 women born between 1 January 1919 and 31 December 1945, resident in Sweden since age 51 yr, from the population registry. Women who died or emigrated before age 61 yr or who had invasive cervical cancer or total hysterectomy before age 61 yr were excluded. Women entered the cohort at age 61 yr and were followed up until a diagnosis of invasive cervical cancer, a total hysterectomy, emigration from Sweden, age 81 yr, death, or 31 December 2011, whichever came first. Cancer cases were identified through the Swedish National Cancer Registry. National linked registries were used for confounding variables (education level, birth cohort). Screening history was from screening registry	Organized cervical screening programme introduced between 1967 and 1977. Every 3 yr for women aged 23–50 yr and every 5 yr for women aged 51–60 yr. Some areas screening women to age 65 yr	Median follow-up time: unscreened, 10.6 yr; screened, 11.4 yr; overall, 10.9 yr Person-yr not given	Cervical cancer incidence after age 60 yr. Data modelled in a competing risk framework (hysterectomy and death as competing events) using screening history at ages 51–60 yr as stratifying variable and first test at age 61–65 yr as exposure of interest Outcome: cervical cancer. Pap tests within 50 d of diagnosis excluded 37% of cohort screened at age 61–65 yr	868 cases of cervical cancer diagnosed at age 61–80 yr	HR for screening at age 61–65 yr stratified by screening status at age 51–60 yr (adjusted for birth cohort, education level) Adequately screened, normal: 0.90 (0.69–1.17) Inadequately screened, normal: 0.82 (0.56–1.22) Unscreened: 0.42 (0.24–0.72) Low-grade abnormality: 0.43 (0.25–0.74) High-grade abnormality: 0.59 (0.36–0.96)	Education level, birth cohort Sensitivity analysis included parity and lifetime diagnosis of COPD as a proxy for smoking status	Extent of benefit from screening women in their 60s varied depending on previous screening history. Provides significant risk reduction for previously unscreened women or women with past abnormalities. Women with normal histories may still benefit from stage shift

Table 4.12   (continued)

Reference Country	Cohort description: no. of women, screening period, source of screening data, and source of follow-up data	Established programme: year of start, screening age, screening interval	Accrual and follow-up periods Person-years	Cervical cancer or precancer end-point, and incidence or mortality age ranges	No. of cases or deaths	Cervical cancer incidence or mortality RR (95% CI)[a]	Adjustments	Comments
Pankakoski et al. (2019) Finland	Cohort of 954 128 women born in 1926–1956 and aged 55–65 yr at the beginning of follow-up, from the population registry Screening history was taken from the screening registry, 1991–2011. Incidence of cervical cancers and deaths in women aged ≥ 55 yr were from the cancer registry Rates were compared with the reference cohort (because uninvited at 65 yr were not Helsinki residents, so had different underlying risk)	Target age 30–60 yr, every 5 yr. Cytology and, since 2012, primary HPV testing has been incorporated into the cervical cancer screening programme. Some use in RCT 2003–2012. Some areas, including Helsinki, invite women to age 65 yr	1991–2014 Median, 11.1 person-yr	Incidence-based mortality risk ratio of cervical cancer for women invited to routine screening at age 65 yr compared with those not invited	No. of cervical cancer deaths: Study cohort (486 869) not invited at age 65 yr, *n* = 212; unadjusted rate, 3.8 per 100 000 Study cohort (59 065) invited (Helsinki) at age 65 yr, *n* = 25; unadjusted rate, also 3.8 per 100 000	Background risk-adjusted RR of death from cervical cancer for women invited at age 65 yr: 0.52 (0.29–0.94), compared with those not invited RR with respect to the uninvited: For women not attending screening: 1.28 (0.65–2.50) For women attending screening: 0.28 (0.13–0.59)	Area of residence (background risk of cervical cancer)	Helsinki area was using cytology. Some areas were using HPV testing Unable to adjust for individual-level hysterectomy

BMI, body mass index; CI, confidence interval; CIS, carcinoma in situ; COPD, chronic obstructive pulmonary disease; d, day or days; HPV, human papillomavirus; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk; yr, year or years.

[a] Data as reported in source, with conversion to reference group of unscreened women where necessary to standardize comparison.

30 years or older, with no cases recorded in this category in those aged 20–29 years. [The Working Group noted that women who were screened twice or more also had significantly lower rates of all cancers, supporting the idea of a healthy participant effect.]

In Denmark, Dugué et al. (2014) aimed to compare all-cause mortality between cervical screening participants and non-participants and included mortality from cervical cancer as an outcome. Using the Danish registry infrastructure, 1 030 786 women resident in Denmark aged 23–51 years on 1 January 1990 and still alive on 31 December 1997 (a period during which all were offered two rounds of screening) were followed up until death, emigration, or 31 December 2010. The hazard ratio for death from cervical cancer for never-screened women compared with regularly screened women was 7.91 (95% CI, 6.62–9.46) and for irregularly screened women compared with regularly screened women was 2.23 (95% CI, 1.81–2.73).

Two cohort studies focused on older women: in Sweden, Wang et al. (2017) examined the protectiveness of screening against cervical cancer incidence in women older than 60 years, complementing the cohort study of Pankakoski et al. (2019) in Finland, which examined the effectiveness of screening against cervical cancer mortality in women older than 65 years.

Wang et al. (2017) used linked registry databases to follow up 569 132 women in Sweden for a median of 10.9 years and examined their screening history at age 51–60 years to determine the impact of being screened at age 61–65 years on cervical cancer incidence at age 61–80 years. After adjusting for birth cohort and education level, they found that the greatest benefit of screening at age 61–65 years, compared with not screening at that age, was in those women who were unscreened at ages 51–60 years or who previously had abnormalities detected. Hazard ratios were as follows: in unscreened women at age 51–60 years, 0.42 (95% CI, 0.24–0.72); in

women with previous low-grade abnormality at age 51–60 years, 0.43 (95% CI, 0.25–0.74); in women with previous high-grade abnormality at age 51–60 years, 0.59 (95% CI, 0.36–0.96). Women with a previous normal history at age 51–60 years had a non-significant reduction in risk through screening at age 61–65 years compared with women with the same history who were not screened. Results were as follows: in women with adequate screening history at age 51–60 years, normal results, 0.90 (95% CI, 0.69–1.17); in women with inadequate screening history at age 51–60 years, normal results, 0.82 (95% CI, 0.56–1.22).

Pankakoski et al. (2019) compared cervical cancer mortality for women in Helsinki offered screening at age 65 years with women from other parts of Finland who were not offered screening at age 65 years but who had been offered routine screening every 5 years from age 30 years to 60 years. The cohort included 954 128 women aged 55–65 years followed up from 1991 to 2011. During the study, most screening was performed using conventional cytology, with small amounts of HPV-based testing during a concurrent RCT. The background risk-adjusted RR of death from cervical cancer for women invited at age 65 years was 0.52 (95% CI, 0.29–0.94), compared with the uninvited. Unsurprisingly, there was an important difference in risk by acceptance of the invitation: for non-attenders, 1.28 (95% CI, 0.65–2.50) and for attenders, 0.28 (95% CI, 0.13–0.59). Self-selection bias may affect these findings (lower-risk women with a history of screening may be more likely to accept the invitation to screen at age 65 years). [The Working Group noted the adequate quality of the study; although women were from different geographical areas, this was adjusted for in the analysis.]

(d)   Case–control studies

Peirson et al. (2013) identified 18 case–control studies (one study had four publications) of adequate quality and suitable outcome

measures to estimate the impact of cytology screening on cervical cancer incidence and to consider age range and screening intervals. The data meta-analysis included almost 4800 cases and 18 000 controls from 12 of the studies, and found lower odds of having undergone screening with cytology in women who were diagnosed with cervical cancer (odds ratio [OR], 0.35; 95% CI, 0.30–0.41; P < 0.00 001) but noted a large degree of heterogeneity. These studies included older data identified through being previously included in two reviews of cervical screening by the United States Preventive Services Task Force. Eleven of these studies were included in the 2005 *IARC Handbooks* review (Aristizabal et al., 1984; Herrero et al., 1992; Sasieni et al., 1996; Hernández-Avila et al., 1998; Jiménez-Pérez & Thomas, 1999; Nieminen et al., 1999; Hoffman et al., 2003; Sasieni et al., 2003) or the 1986 IARC review (Clarke & Anderson, 1979; La Vecchia et al., 1984; Berrino et al., 1986; IARC, 1986). Four additional studies identified by Peirson et al. (2013) (Makino et al., 1995; Talbott et al., 1995; Andrae et al., 2008; Decker et al., 2009), four studies identified but not included in the overall estimate of effect by Peirson et al. (2013) (Zappa et al., 2004; Yang et al., 2008; Sasieni et al., 2009; Kasinpila et al., 2011), and nine studies identified from further literature review (Murillo et al., 2009; Lönnberg et al., 2012; Nascimento et al., 2012; Kamineni et al., 2013; Castañón et al., 2014; Vicus et al., 2015; Rosenblatt et al., 2016; Lei et al., 2019; Wang et al., 2020) are summarized below and in Table 4.13 (web only; available from https://publications.iarc.fr/604); these studies add to the consistency of the literature supporting the effectiveness of cytology-based screening in preventing cervical cancer development and death. Three further case–control studies used mortality as an outcome (Lönnberg et al., 2013; Rustagi et al., 2014; Vicus et al., 2014). The available case–control studies are a mixture of population-based studies using administrative data sets, which avoid participation and

recall biases, and studies based on recruitment invitations, which probably suffer from these biases but obtain detailed information to adjust for confounders. Each study has strengths and weaknesses in attempting to estimate the true underlying effect; however, the overall consistency of findings is reassuring, in particular from the studies of Lönnberg et al. (2012, 2013), which examine both incidence and mortality, and attempt to adjust for self-selection bias.

Makino et al. (1995) studied the relationship of screening history with diagnosis of invasive cervical cancer using a case–control design including 198 cases of invasive cervical cancer diagnosed in 1984–1990 in Miyagi, Japan, each matched with two controls by age and area. They divided the cases into those that were detected by screening, who were assigned controls from screening programme records, and those that were diagnosed as outpatients, who were matched with other gynaecological outpatients. They determined ever-screened status using programme records or, if a woman reported on a questionnaire that she was screened elsewhere, accepted self-report. They excluded women with a history of abnormal screening results; it is unclear whether this exclusion applies to both cases and controls and the impact it will have on the correct assignment of whether a woman has ever been screened compared with the underlying population. They found a protective OR of 0.14 (95% CI, 0.088–0.230) for ever being screened, consistent across the age ranges 34–49 years and 50–74 years. [The Working Group noted that the limitations of this study – the exclusion of women with abnormal screening results and the acceptance of self-report – may have resulted in an overestimate of the true effect of screening.]

Talbott et al. (1995) examined self-reported screening history from cases of invasive cervical cancer sourced from the Pennsylvania Cancer Registry and age- or area-matched controls. Because screening history was obtained from consent-based interviews up to 2 years after

diagnosis, only 143 women (30% of cases) with a matched control were included in the final analysis (ages 25–79 years), resulting in cases with an earlier stage of disease than the source sample. Although it acknowledged both selection bias and likely recall bias, the study estimated an OR of no Pap test in the previous 3 years of 3.10 (95% CI, 1.45–6.64), adjusted for smoking status, marital status, income, physician's visit within 3 years, number of pregnancies, age at first pregnancy, number of long-term relationships, use of birth control, and use of condoms. [The Working Group noted that the findings should be interpreted with caution because of the poor participation rate of cases; cases with advanced disease at diagnosis were systematically underrepresented.]

Zappa et al. (2004) examined the screening history of 208 cases of invasive cervical cancer in women aged 70 years or younger at diagnosis between 1994 and 1999 and 832 age-matched controls in Florence, Italy. The study aimed to assess the impact of screening on the incidence of adenocarcinoma compared with squamous cancers, and the impact of screening by age in women younger than or older than 40 years. High-grade CIN and cancers were identified through the Tuscany Tumour Registry, and screening history was collected from a computerized archive estimated to contain about two thirds of all the screening tests in the area. Smears taken in the 12 months before the index date of the case were excluded. Four randomly selected controls with no record of hysterectomy and who were resident for at least 5 years in the area per case (matched on year of birth) were selected from the municipality residence database. After adjustment for civil status and birthplace, screening was found to be protective against cervical cancer (< 3 years since last test: OR, 0.25; 95% CI, 0.15–0.42; 3–< 6 years since last test: OR, 0.34; 95% CI, 0.21–0.56); ≥ 6 years since last test: OR, 0.56; 95% CI, 0.38–0.82). However, no significant protection was observed

for adenocarcinomas alone (< 3 years since last test: OR, 0.65; 95% CI, 0.26–1.65), and women older than 40 years had stronger and more consistent protection against SCCs over time from screening.

Andrae et al. (2008) assessed all 1230 invasive cervical cancer cases diagnosed in Sweden between 1999 and 2001 against the screening history in the previous 6 years of five population-based age-matched controls per case (6124 total). All data were obtained from population-based linked data registries, avoiding recall or selection bias. Women who had not been screened in the recommended interval for their age had higher odds of cervical cancer (OR, 2.52; 95% CI, 2.19–2.91), with consistent findings across age groups. Screening was also protective against non-SCC cancers (SCC: OR, 2.97; 95% CI, 2.51–3.50; non-SCC: OR, 1.59; 95% CI, 1.20–2.11).

Yang et al. (2008) undertook a case–control study in New South Wales, Australia, where biennial cytology screening was recommended for women aged 20–69 years. Data on 877 cases diagnosed with invasive cervical cancer between 2000 and 2003 were obtained from the cancer registry and controls from the Pap Test Register, which contains almost all screening results. However, to have a record in the Pap Test Register a woman needs to have been screened at least once. [The Working Group noted that this may have led to the 2614 age-matched controls being more likely to have been screened than the general population from which the cases were drawn, which could bias estimates in favour of screening being protective. Therefore, the study findings are applicable to screened women rather than to the general population.] The exposure of interest was screening in the 4-year period before diagnosis, and results were adjusted for the result of the first Pap test in the previous 6 years. Compared with no screening in the previous 4 years, irregular screening had an OR of 0.189 (95% CI, 0.134–0.265) and regular screening

had an OR of 0.065 (95% CI, 0.044–0.096). If restricted only to cases with any screening history on the screening registry, to match selection criteria with controls, estimates were attenuated somewhat: irregular screening OR, 0.215 (95% CI, 0.150–0.309), regular screening OR, 0.070 (95% CI, 0.046–0.106). Results were consistent across 10-year age groups and for both SCC and non-SCC cancers.

In Manitoba, Canada, Decker et al. (2009) compared screening in the previous 5 years from administrative claims between 666 cervical cancer cases aged 18 years or older notified to the cancer registry in 1989–2001 and 3343 age- and area-matched controls (5 per case) sourced from a state-wide universal health insurance register. Women who had not had a Pap test in the previous 5 years had higher odds of cervical cancer (OR, 2.77; 95% CI, 2.30–3.30).

In a case–control study in four areas of Colombia, Murillo et al. (2009) enrolled 200 cases aged 25–69 years from pathology records and 200 age- and neighbourhood-matched controls. Screening history was compiled using blinded review, excluding diagnostic smears, and nurses conducted structured risk factor interviews. After adjustment for age at first intercourse, age at first birth, parity, use of oral contraceptives, number of sexual partners, insurance status, and literacy, the OR for cervical cancer in women who had no screening in the previous 36 months was 3.54 (95% CI, 2.01–6.24).

Sasieni et al. (2009) described findings by histological type using their previous population-based case–control study in a data audit of women aged 20–69 years using the routine cytology database in the United Kingdom (Sasieni et al., 1996, 2003). Using data from 3305 cases and 6516 controls, they found that screening within 10 years of diagnosis provided greater protection against SCC and adenosquamous cancers than against adenocarcinoma (adenocarcinoma: OR, 0.72; 95% CI, 0.54–0.95;

SCC: OR, 0.37; 95% CI, 0.32–0.41; adenosquamous cancer: OR, 0.25; 95% CI, 0.15–0.43).

In a hospital-based case–control study in Thailand, Kasinpila et al. (2011) compared 130 women aged 30–64 years diagnosed with invasive cervical cancer in four tertiary hospitals with age-matched controls who were patients or visitors at the same hospitals. Screening history and risk factor information were collected by structured interview. After adjusting for age at first intercourse, alcohol consumption, and use of oral contraceptives, they found that any number of tests more than 6 months before the diagnosis date was protective (for 1–5 tests: OR, 0.45; 95% CI, 0.25–0.84; for ≥ 6 tests: OR, 0.29; 95% CI, 0.11–0.82) and that more recent tests were more protective (test in previous 1–2 years: OR, 0.27; 95% CI, 0.13–0.56; test ≥ 3 years ago: OR, 0.42; 95% CI, 0.20–0.88).

The study of Lönnberg et al. (2012) in Finland compared screening in 1546 cervical cancer cases and 9276 age-matched controls using cancer registry, screening registry, and population registry data to avoid selection and recall biases. A statistical adjustment was made to correct for self-selection bias. The estimated association between cervical cancer and screening participation was significant across stage and cancer types (OR, 0.53; 95% CI, 0.46–0.62) and was statistically significant in the individual 5-year age bands between the ages of 40 years and 64 years and in the 15-year age bands of 40–54 years (OR, 0.44; 95% CI, 0.35–0.56) and 55–69 years (OR, 0.37; 95% CI, 0.27–0.52), with a smaller impact in the 25–39 year age group (OR, 0.81; 95% CI, 0.63–1.05).

In a hospital-based case–control study in Rio de Janeiro, Brazil, Nascimento et al. (2012) compared 152 cases with 169 age- and area-matched controls who were visitors to the same hospital. The researchers used a consent-based model and comprehensive risk factor survey to gather screening and other history, recruiting 152 of 169 (89.8%) of eligible cases aged 25–68 years,

90% of whom had SCC. After adjustment for education level, age, municipality, and tobacco use, it was found that reporting three or more Pap tests 3 years before the index date was associated with a lower odds of cervical cancer (OR, 0.16; 95% CI, 0.074–0.384).

Kamineni et al. (2013) assessed the effectiveness of screening women aged 55–79 years in a case–control study in the USA involving 69 cases of invasive cervical cancer and 208 age-matched controls. Women were members of one of two large health insurers, and screening and medical or demographic history for 7 years before the case diagnosis date was obtained through medical record review. After adjustment for age and smoking status, the OR for cervical cancer in those screened 1 year previously (estimated duration of occult phase) was 0.23 (95% CI, 0.11–0.44). The greatest reduction in risk was observed in the year after screening; the incidence returned to that in unscreened women 5–7 years after a negative screen test result.

In the accompanying case–control study of the impact of screening on cervical cancer mortality, Lönnberg et al. (2013) analysed the screening history of 506 women who died in the period 2000–2009 and 3036 age-matched population-based controls. After adjustment for self-selection bias, the results showed a protective effect of an index screen (defined as the last age group invitation and possible screening test within the 66 months before the diagnosis), with an OR of 0.34 (95% CI, 0.14–0.49). No protective effect on mortality from adenocarcinoma was detected, and the effect on mortality was lowest for those aged 25–39 years (OR, 0.70; 95% CI, 0.33–1.48).

Castañón et al. (2014) conducted a population-based case–control study in England and Wales to consider the effect of screening women aged 50–64 years on the incidence of cervical cancer in women aged 65 years or older. The study included 1341 cases diagnosed between 2007 and 2012 and 2646 age-matched controls

(two per case, including one from the same general practice). Screening with an interval of < 5.5 years compared with no screening in women aged 50–64 years resulted in an OR for cervical cancer after age 65 years of 0.25 (95% CI, 0.21–0.30). Protection decreased with time since last screen, and the estimated absolute risks over time for the population who were screened at age 50–64 years supported the conclusion that there was low risk in women with adequate negative screening and justified cessation of screening at age 65 years for this group.

Rustagi et al. (2014) conducted a case–control study in the USA in health-care enrolees aged 55–79 years, to assess the effect of screening on cervical cancer mortality in older women. Women who had died from cervical cancer between 1980 and 2010 ($n = 39$) were matched to two controls each ($n = 80$) by health plan, age, and duration of health plan enrolment. Screening in the 7 years before the index date was protective against cervical cancer death (OR, 0.26; 95% CI, 0.10–0.63) after adjustment for matching characteristics, smoking status, marital status, and race or ethnicity.

Vicus et al. (2014) analysed the mortality from cervical cancer and the effectiveness of cytology screening by age group in 1052 cases and 10 494 controls aged 20–69 years diagnosed between 1998 and 2008 in Ontario, Canada. State-wide administrative data sets were used to obtain screening history and to obtain age-matched, income-matched controls, and cases were identified from the cancer registry. Screening 3–36 months before the date of diagnosis was found to be protective in all age groups 30 years or older (ORs from 0.28 to 0.60). In a related analysis of incidence, using 5047 cases and 10 094 controls, Vicus et al. (2015) detected a significant protective effect of screening 3–36 months before the date of diagnosis only in the age groups 40–44 years (OR, 0.82; 95% CI, 0.69–0.97), 50–54 years (OR, 0.59; 95% CI, 0.48–0.73), 55–59 years (OR, 0.52; 95% CI,

0.48–0.73), and 60–64 years (OR, 0.59; 95% CI, 0.46–0.76).

[Rosenblatt et al. (2016)](#) examined the effect of cervical screening from age 65 years for up to 7 years between 1991 and 1999 in a population from 11 areas of the USA, using Medicare insurance claims data and Surveillance, Epidemiology, and End Results cancer registry data. The study identified 1267 cases, and these were matched to 10 137 controls (up to 8 controls per case) on age and geographical location. Data on previous hysterectomy were not available for controls, but population-based data were used to estimate the effect on risk of removal of hysterectomized controls. After adjustment for race and postal code-level income, the results suggested that having a Pap test 2–7 years before diagnosis provided significant protection against cervical cancer (OR, 0.64; 95% CI, 0.53–0.78). After adjustment also for the likely prevalence of hysterectomy in controls, the protective effect of screening increased (OR, 0.38; 95% CI, 0.32–0.46). Effectiveness was seen across the age range but was greatest in women aged 65–74 years (hysterectomy-adjusted OR, 0.24; 95% CI, 0.15–0.37), women aged 75–84 years (hysterectomy-adjusted OR, 0.44; 95% CI, 0.34–0.55), and women aged 85–100 years (hysterectomy-adjusted OR, 0.44; 95% CI, 0.29–0.66). In women aged 72 years and older who had complete exposure data for the ascertainment period 1991–1999, the greatest effects were seen in preventing squamous carcinoma (hysterectomy-adjusted OR, 0.31; 95% CI, 0.23–0.40), regional disease (hysterectomy-adjusted OR, 0.27; 95% CI, 0.20–0.39), and distant disease (hysterectomy-adjusted OR, 0.30; 95% CI, 0.16–0.58). [The Working Group noted that the main limitation of this study is that the determinants of screening participation in this age group in this setting are not known. Routine screening was not recommended in previously screened older women during this period, although 3-yearly screening was funded by Medicare. Previous screening history before age 65 years was not available. The results may therefore not be applicable to a general population for which routine screening is recommended.]

[Lei et al. (2019)](#) conducted a population-based nested case–control study in Sweden using the linked population registry infrastructure to examine whether cytology screening has a protective effect on the incidence of adenosquamous cancer and rare types of invasive cervical cancer (RICC) (e.g. clear cell carcinoma, large cell carcinoma, glassy cell carcinoma, neuroendocrine carcinoma). Cases of invasive cervical cancer diagnosed in Sweden in 2002–2011 were identified from the Swedish Cancer Registry and underwent clinical and histopathological review, which resulted in the identification of 338 cases of adenosquamous cancer (49%) and RICC (51%). For each case, 30 controls without hysterectomy or history of cervical cancer and who were alive and living in Sweden at the date of diagnosis of the case were selected from the total population register using incidence density sampling and matched on year of birth. Cervical screening data from the previous two screening rounds (women aged 30 years or older were included to enable two screening rounds) were obtained from the national screening registry, and tests within 6 months of the date of diagnosis of the case were excluded. ORs were interpreted as incidence rate ratios. After adjustment for education level, two screening tests compared with none was associated with a substantially lower risk of adenosquamous cancer (IRR, 0.22; 95% CI, 0.14–0.34) and RICC (IRR, 0.34; 95% CI, 0.21–0.55). Protection was greatest for those aged 30–60 years, for adenosquamous cancers, with two tests compared with one, and against more advanced cancers. Protection was seen for both HPV-positive and HPV-negative cancers and across rare cancer types.

[Wang et al. (2020)](#) undertook an audit of the Swedish cervical screening programme and presented a population-based nested case–control analysis of cervical cancer risk by screening

status. The authors used the same methods as Lei et al. (2019) but included all cervical cancer cases (*n* = 4254) and 120 006 controls. Women aged 26–28 years had one screening round examined. Women with no screening tests compared with women who had been screened in the last two rounds had an OR of 4.1 (95% CI, 3.8–4.5) for cervical cancer. Attending one of the two last screens only lowered the odds ratio somewhat (women who missed the last screening round but attended the screening round before: OR, 2.4; 95% CI, 2.2–2.7; women who attended the last screening round but missed the one before: OR, 1.6; 95% CI, 1.5–1.8).

(e) Screening intervals and age range for screening

The Peirson et al. (2013) meta-analysis examined the evidence from 14 studies, including two cohort studies (Herbert et al., 1996; Rebolj et al., 2009) and 12 case–control studies (La Vecchia et al., 1984; Berrino et al., 1986; Herrero et al., 1992; Makino et al., 1995; Sasieni et al., 1996, 2003, 2009; Jiménez-Pérez & Thomas, 1999; Hoffman et al., 2003; Miller et al., 2003; Zappa et al., 2004; Andrae et al., 2008; Yang et al., 2008; Kasinpila et al., 2011), to review screening intervals for protection against incident cervical cancer. The meta-analysis also included four studies that considered ages of commencement and cessation of screening: three case–control studies (Sasieni et al., 1996, 2003, 2009; Hoffman et al., 2003; Andrae et al., 2008) and one cohort study (Rebolj et al., 2009). Differences in study designs prevented any pooling of data to analyse screening intervals, but the review had four key consistent findings: (i) the shortest time interval since the last screen in each study consistently had the highest degree of protection associated with it, (ii) screening intervals of 5 years or less consistently appear to offer protection, (iii) longer intervals between screens provide diminishing protection, but (iv) any history of screening is more protective than no history of screening.

No data pooling was possible in examining ages of commencement and cessation of screening. The evidence suggested that screening in women younger than 30 years may be less effective, but evidence is strong for a beneficial effect in women older than 30 years, including in women aged 65 years or older. The more recent data reviewed above support these conclusions that more recent screening confers greater protection, that screening in women younger than 30 years may be of more limited benefit (Lönnberg et al., 2012, 2013; Vicus et al., 2014, 2015), and that there is evidence for the effectiveness of screening older women, noting that women who have not been screened regularly, or who have had previous abnormal screening results, are likely to benefit most from screening at older ages (Kamineni et al., 2013; Castañón et al., 2014; Rustagi et al., 2014; Rosenblatt et al., 2016; Wang et al., 2017; Pankakoski et al., 2019).

4.3.3 Beneficial effects of screening using LBC

(a) Accuracy of LBC compared with conventional cytology

Several systematic reviews and meta-analyses have been published providing estimates of the sensitivity and specificity of LBC and comparing the sensitivity, specificity, and PPV of LBC systems with those of conventional cervical testing in terms of their ability to identify biopsy-confirmed CIN2 or CIN3 (Austin & Ramzy, 1998; Payne et al., 2000; Bernstein et al., 2001; Sulik et al., 2001; Davey et al., 2006; Arbyn et al., 2008b; Whitlock et al., 2011; Chen et al., 2012; Fokom-Domgue et al., 2015; Mustafa et al., 2016). Both techniques are based on the same principles to identify precancerous lesions, using the same staining and interpretation methods and almost identical sampling methods.

Most early studies used a paired-sample design, with either split samples or direct-to-vial sampling. In the split-sample method, the conventional slide is made first, and then the

brush and/or spatula is rinsed in the medium for LBC to collect the remaining cells. In the direct-to-vial sampling method, a dedicated sample is collected for LBC by rinsing the spatula and/or brush in the vial containing the liquid medium; a separate sample for conventional cytology is taken before or after the LBC sample. Both methods may introduce some biases. For example, in split samples, the LBC component, which uses the residual sample after smearing for the conventional slide, systematically starts with less cellular material. In direct-to-vial studies, samples for conventional cytology and LBC are taken separately, and if the two samples are taken close together in time, the second sample will take cells from a cervix that has already been scraped, possibly with less cellular material and a higher probability of bleeding, whereas if the two samples are taken at distant time points, they could reflect different conditions of the cervix (i.e. the lesions could evolve or new lesions could emerge) (Cheung et al., 2003; Colgan et al., 2004; Fremont-Smith et al., 2004). Randomizing the order of sampling could avoid this bias.

Most early studies included relatively small numbers of women, and in order to have enough statistical power to estimate sensitivity, they could not recruit samples from the screening population but needed to include in their study population more women with CIN2+, usually including those referred for colposcopy. This selection may introduce a bias by selecting women who had a recent positive test with the technique used at that time in the screening programme (usually conventional cytology), thus overestimating both conventional cytology true-positive and false-positive results, as was discussed by some authors of these early studies (Confortini et al., 2004). Under certain conditions, these studies could accurately estimate sensitivity and, with the limitation explained below, specificity, but they could not estimate the referral rate that would be experienced in a screening population and consequently the PPV. When using a cytology

positivity threshold of ASC-US or worse or LSIL or worse, the cytologist is looking for the cytological signs of a risk factor for the clinically relevant lesions (i.e. HPV infection) and not only for the lesion itself (i.e. CIN2+). Consequently, the test is also dependent upon the underlying prevalence of HPV infection in the tested population for its accuracy. In particular, the specificity of the test decreases when the prevalence of HPV infection increases (Giorgi Rossi et al., 2012).

The quality of the primary studies varied, and most studies had methodological deficiencies and inadequate follow-up (Nanda et al., 2000; Sulik et al., 2001; Davey et al., 2006). In particular, in their systematic review Davey et al. (2006) found that studies of high methodological quality with lower risk of bias estimated very similar sensitivities for LBC and conventional cytology, whereas low-quality studies estimated slightly higher sensitivity for LBC. Similarly, Arbyn et al. (2008b) estimated a pooled sensitivity for LBC of 90.4% (95% CI, 82.5–95.0%) when ASC-US was the threshold and 79.1% (95% CI, 70.1–86.0%) when LSIL was the threshold. For conventional cytology, the pooled sensitivity was 88.2% (95% CI, 80.2–93.2%) when ASC-US was the threshold and 75.6% (95% CI, 66.5–83.0%) when LSIL was the threshold. Therefore, the relative sensitivity estimate for LBC versus conventional cytology was close to 1: 1.03 (95% CI, 0.97–1.09) for an ASC-US threshold and 1.03 (95% CI, 0.96–1.11) for an LSIL threshold. Specificity was higher for conventional cytology when ASC-US was used as the threshold (relative specificity LBC vs conventional cytology, 0.91; 95% CI, 0.84–0.98) and similar when LSIL was used as the threshold (relative specificity LBC vs conventional cytology, 0.97; 95% CI, 0.94–1.01). In their systematic review on HPV test accuracy, Koliopoulos et al. (2017) produced estimates of the absolute sensitivity and specificity of conventional cytology and LBC in studies where cytology was compared with HPV testing. In this review, both cytological methods had lower

sensitivity compared with previous studies: when ASC-US was used as the test threshold, the pooled sensitivity for conventional cytology was 65.9% (95% CI, 54.9–75.3%) for the detection of CIN2+ and 70.3% (95% CI, 57.9–80.3%) for the detection of CIN3+; with the same threshold, the pooled sensitivity for LBC was 75.5% (95% CI, 66.6–82.7%) for the detection of CIN2+ and 70.3% (95% CI, 57.9–80.9%) for the detection of CIN3+. However, the pooled specificity was higher for conventional cytology than for LBC. [To estimate the absolute sensitivity and specificity, colposcopic assessment is required for all subjects to confirm histological diagnosis as a reference standard (Branca & Longatto-Filho, 2015), and because this recent systematic review included studies without systematic assessment of all women, verification bias could not be completely excluded (Fokom-Domgue et al., 2015; Mustafa et al., 2016; Koliopoulos et al., 2017). Furthermore, these estimates come from different studies for conventional cytology and LBC, so the estimates cannot be directly compared.]

Larger studies in low-risk populations, often nested in routine screening programmes, started in the first decade of the 2000s. Some of these studies used a paired-sample design, mostly split samples (Coste et al., 2003; Almonte et al., 2007; Davey et al., 2007; Halford et al., 2010; Tanabodee et al., 2015); others were controlled trials, either individually randomized (Obwegeser & Brack, 2001; Ronco et al., 2007; Maccallini et al., 2008; Sykes et al., 2008) or cluster-randomized (Taylor et al., 2006; Strander et al., 2007; Siebers et al., 2009; Klug et al., 2013). Finally, others were pilot population-based studies with historical or concurrent non-randomized controls (Beerman et al., 2009; Akamatsu et al., 2012; Sigurdsson, 2013; Rebolj et al., 2015; Rozemeijer et al., 2016, 2017; Ito et al., 2020).

(b) Evidence on relative detection and relative PPV from RCTs

In an RCT, the target population is divided into two groups, whose background is expected to have the same characteristics, aside from random fluctuations (Ronco et al., 2007). In large population-based randomized studies, usually only women with a positive test result are assessed. It is therefore impossible to compute absolute sensitivity and specificity. Nevertheless, in this setting, relative detection is a correct estimator of relative sensitivity, and relative referral rate for assessment and relative PPV measure how the specificity of the two tests affects screening efficiency.

Eight RCTs were conducted (Table 4.14) with varying test thresholds and outcomes; seven reported results using ASC-US as the test threshold (Obwegeser & Brack, 2001; Taylor et al., 2006; Ronco et al., 2007; Strander et al., 2007; Maccallini et al., 2008; Sykes et al., 2008; Siebers et al., 2009), and four reported data for an LSIL threshold (Taylor et al., 2006; Ronco et al., 2007; Strander et al., 2007; Klug et al., 2013; Table 4.15).

In a study in a high-risk population in South Africa, Taylor et al. (2006) included colposcopic assessment for all women, which enabled the estimation of the absolute sensitivity and specificity for conventional cytology and LBC. The authors calculated the sensitivity and specificity for conventional cytology and LBC. The sensitivity of conventional cytology for the detection of CIN2+ was 83.6% (95% CI, 71.2–92.2%), with a specificity of 85.1% (95% CI, 83.6–86.5%); the sensitivity of LBC for the detection of CIN2+ was 70.6% (95% CI, 58.3–81.0%), with a specificity of 84.8% (95% CI, 83.5–86.1%).

The only other RCT with colposcopic assessment for all women was conducted in New Zealand (Sykes et al., 2008). In this study, women referred to a colposcopy clinic were randomized to LBC or conventional cytology. The study cannot give information on referral and PPV,

but gave a rather precise estimate of the relative sensitivity: 1.0 (95% CI, 0.83–1.21). [The Working Group noted a low risk of bias in this study.]

The study by Obwegeser & Brack (2001) in Switzerland recruited women of any age attending gynaecology services for opportunistic screening, including women in age ranges for which screening is not recommended. These findings should be interpreted with caution because the only published report included only the assessment of women with high-grade cytological lesions, whereas assessment of women with ASC-US and LSIL was not yet available. LBC classified a higher proportion of women as having LSIL (4.7%) than did conventional cytology (3.7%). The authors found no effect on sensitivity. [The Working Group noted a high risk of bias in this study.]

The study of Ronco et al. (2007) in Italy randomized women to LBC plus HPV testing or to conventional cytology. The study also enabled a comparison between the baseline results for LBC alone versus conventional cytology, because the LBC reading was performed blinded to the HPV test result, although colposcopy was not performed blinded to the HPV test result, which could be expected to increase the index of suspicion for the colposcopist. When the ASC-US threshold was used, the study found a small, non-significant increase in the CIN2+ detection rate using LBC, but not in the CIN3+ detection rate, and the PPV was much lower with LBC than with conventional cytology. When the LSIL threshold was used, LBC had a non-significantly lower detection rate and a similar PPV. [The Working Group noted some concern of bias in this study.]

The study of Strander et al. (2007) in Sweden allocated women to LBC or conventional cytology by randomization of the week of the scheduled appointment. The outcome (CIN2+) was assessed with passive follow-up through the pathology registry, without knowing how the women were individually managed. A 60% increase in detection using LBC was found, with a similar PPV. However, the results should be interpreted with caution given that some imbalance in randomization occurred, because adjusting for age and screening centre produced substantially different ORs compared with unadjusted figures. [The Working Group noted some concern of bias in this study.]

A small RCT in Italy (Maccallini et al., 2008) found no difference in either relative detection or relative PPV but reported strong heterogeneity between centres for relative PPV. The authors noted a higher compliance to colposcopy in the LBC group than in the conventional cytology group, and adjustment for non-compliance reduced the difference in detection between the two groups. [The Working Group noted some concern of bias in this study.]

The largest RCT was conducted in the Netherlands and randomized about 90 000 women (Siebers et al., 2009). The study raised no concerns about randomization and ascertainment procedures, and the sample size enabled precise estimates to be obtained. The authors found similar detection rates for CIN2+ and CIN3+ (CIN2+ relative detection rate, 1.00; 95% CI, 0.84–1.20; CIN3+ relative detection rate, 1.05; 95% CI, 0.86–1.29) and similar PPVs (relative PPV, 0.99; 95% CI, 0.80–1.22) in the two groups. [The Working Group noted a low risk of bias in this study.]

Klug et al. (2013) randomized 20 practices in Germany to use LBC or conventional cytology. The study also included the use of computer-assisted technology in addition to LBC, but results were given separately for manual reading and computer-assisted reading. Nevertheless, the use of computer-assisted reading was used to centralize LBC reading in one laboratory, and conventional cytology was read in nine different laboratories. In Germany the standard cytology classification is the Munich II nomenclature (Hilgarth, 2001). This is the only RCT that reported a more than 2-fold increase in detection rate with LBC

Table 4.14 Study characteristics of randomized controlled trials comparing cervical cancer screening by liquid-based cytology versus conventional cytology

Reference Trial, country	Randomization	No. of women	Population	Age at entry (years)	LBC procedure	Reference standard	Blinding of histological assessment?	Reported end-points	Long-term outcomes
Obwegeser & Brack (2001) Switzerland	Individual	Conv.: 1002 LBC: 997	Opportunistic screening	15–≥ 70	ThinPrep 2000	Colposcopy for women with HSIL cytology; for ASC-US and LSIL, follow-up was mostly incomplete	No	CIN2+	NR
Taylor et al. (2006) South Africa	No; practice rotating every 6 mo	Conv.: 2444 LBC: 3114	High-risk population	35–65	ThinPrep 2000	Colposcopy for all women	Yes	CIN2+ CIN3+	Not possible. Women were all referred for colposcopy
Ronco et al. (2007) NTCC, Italy	Individual	Conv.: 22 466 LBC: 22 708	Screening	25–60	ThinPrep	Colposcopy for all positive	CIN reviewed blindly	CIN2+ CIN3+	Not possible. Women were managed according to HPV test results
Strander et al. (2007) Sweden	Randomized per week of appointment	Conv.: 8810 LBC: 4674	Screening	23–60	ThinPrep 2000	Referral as routine practice; histology searched through registries	Yes	CIN2+	Cumulative incidence up to 3 yr and 7 mo
Sykes et al. (2008) New Zealand	Individual	Conv.: 453 LBC: 451	Women in colposcopy clinics	16–75	SurePath	Colposcopy-guided biopsy	No	CIN2+	NR
Maccallini et al. (2008) Italy	Individual	Conv.: 4299 LBC: 4355	Screening	25–64	ThinPrep	Colposcopy for all positive	No	CIN2+ CIN3+	NR
Siebers et al. (2008, 2009) NETHCON, Netherlands	Cluster RCT; family practice as randomization unit	Conv.: 40 562 LBC: 49 222	Screening	25–60	ThinPrep 3000	Referral as routine practice. All follow-up tests blindly reviewed	Yes	CIN2+ CIN3+	NR
Klug et al. (2013) Germany	Randomized per week of visit	Conv.: 9352 LBC: 11 555	Opportunistic screening	≥ 20	ThinPrep with/without Imaging System	Colposcopy for all women with LSIL+	No	CIN2+ CIN3+	NR

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; Conv., conventional cytology; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesion; mo, month or months; NETHCON, Netherlands ThinPrep versus Conventional Cytology Trial; NTCC, New Technologies for Cervical Cancer Screening; NR, not reported; RCT, randomized controlled trial; yr, year or years.

Table 4.15 Comparison of test performance between liquid-based cytology and conventional cytology in randomized controlled trials

Reference Country	Age (years)	Threshold	Total number		Detection rate (%)		PPV (%)	Unsatisfactory cytology
					Outcome: CIN2+	Outcome: CIN3+	Outcome: CIN2+	
			Conv.	LBC	RR (95% CI)[a]	RR (95% CI)	RR (95% CI)[a]	RR (95% CI)
Obwegeser & Brack (2001) Switzerland	15–≥ 70	ASC-US	1002	997	0.92 (0.41–2.07)[b]	NA	NA	NA
Taylor et al. (2006) South Africa	35–65	ASC-US	2444	3114	0.81 (0.54–1.21)	0.67 (0.39–1.14)	0.83 (0.56–1.21)	2.85 (1.72–4.72)
Strander et al. (2007) Sweden	23–60	LSIL	8810	4674	1.63 (1.09–2.43)	NA	1.02 (0.75–1.40)	NA
Ronco et al. (2007) Italy	25–60	ASC-US	22 466	22 708	1.17 (0.87–1.56)	0.84 (0.56–1.25)	0.58 (0.44–0.77)	0.62 (0.56–0.69)
Ronco et al. (2007) Italy	25–60	LSIL	22 466	22 708	1.03 (0.74–1.43)	0.72 (0.46–1.13)	0.58 (0.43–0.78)	NA
Strander et al. (2007) Sweden	23–60	ASC-US	8810	4674	1.40 (0.99–1.98)	NA	0.99 (0.74–1.33)	0.47 (0.27–0.82)
Maccallini et al. (2008) Italy	26–64	ASC-US	4299	4182	1.24 (0.72–2.15)	NA	1.40 (0.84–2.33)	0.31 (0.23–0.42)
Sykes et al. (2008) New Zealand	16–75	ASC-US	453	451	1.00 (0.83–1.21)	NA	NA	0.29 (0.16–0.55)
Siebers et al. (2008) Netherlands	30–60	ASC-US	40 047	48 941	1.00 (0.84–1.20)	1.05 (0.86–1.29)	0.99 (0.80–1.22)	NA
Siebers et al. (2009) Netherlands	30–60	ASC-US	40 047	48 941	NA	NA	1.03 (0.66–1.78)	NA
Klug et al. (2013) Germany	≥ 20	LSIL	9296	11 331	2.74 (1.66–4.53)	2.87 (1.55–5.32)	1.17 (0.81–1.67)	7.18 (2.55–20.2)

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; Conv., conventional cytology; LBC, liquid-based cytology; LSIL low-grade squamous intraepithelial lesion; NA, not available; PPV, positive predictive value; RR, relative risk.

[a] RR and 95% CI are reported as computed by the authors in main analyses, including adjustment procedures.

[b] Authors did not report relative measures or 95% CI; these have been computed from raw data by the Working Group.

compared with conventional cytology for both CIN2+ and CIN3+. The PPV was similar in the two groups. The authors only reported detection for LSIL+, and most of the abnormal cytology results, particularly for conventional cytology, were ASC-US. Surprisingly, the authors reported almost no unsatisfactory samples using conventional cytology. [The Working Group noted a high risk of bias in this study, and concern about generalizability.]

In RCTs, as well as in paired studies with unbiased assessment, LBC had a slightly higher sensitivity for detection of CIN2+ compared with conventional cytology; the difference in sensitivity, if any, in some studies seemed to be smaller for detection of CIN3+. This result in relation to sensitivity is consistent with that obtained in two very large population-based split-sample studies (Davey et al., 2007; Halford et al., 2010), which were not included in the systematic reviews on accuracy reported in the previous paragraph, because of incomplete assessment. In contrast, conventional cytology in most contexts had higher specificity for correctly classifying CIN1 or less severe conditions as negative, particularly when ASC-US was the test threshold, whereas the difference was smaller when LSIL was the test threshold. Because of this, the PPV was lower for LBC in many studies. Finally, a reduction in the proportion of unsatisfactory slides using LBC was reported in all studies, except for the study by Klug et al. (2013).

There is heterogeneity between studies, as is expected when comparing two tests that require expertise and training and for which not all countries use the same classification system. As reported before, the specificity of cytological tests at the threshold of ASC-US or LSIL is influenced by the prevalence of HPV infection in the tested population; this may explain part of the heterogeneity (Davey et al., 2006).

(c) Evidence on the effect of LBC on screening performance

Results from population-based studies have not always confirmed the data from randomized and paired-sample cross-sectional diagnostic accuracy studies. A summary of the characteristics of studies evaluating the effect that the introduction of LBC has had on screening performance and its effectiveness is reported in Table 4.16, and Table 4.17 summarizes the main results of comparisons between the performance of LBC and that of conventional cytology.

In England, Blanks & Kelly (2010) used aggregated routine quality assurance data from screening laboratories and reported an increase in PPV and a reduction in variability between laboratories after the introduction of LBC. Although differences observed in before-and-after studies may be due to other factors that changed concomitantly, this study compared a large number of laboratories and also investigated an outcome (variability between laboratories) that is directly linked to the introduction of the technology, but which should not be linked to trends in epidemiology or in differences in the screened population, making the causal link more plausible. [The Working Group noted adequate methodology in this study.]

In Iceland, Sigurdsson (2013) compared the results of LBC with conventional cytology in 2007–2011, when the organized screening programme shifted to LBC and other laboratories still used conventional cytology. The authors found no increase in the detection of CIN2+ or of CIN3+ in women younger than 40 years. In women older than 40 years there was a small, non-significant decrease in CIN3+ detection, whereas CIN2+ detection was similar in conventional cytology and LBC. The PPV of LBC was similar to or slightly higher than that of conventional cytology. The authors tried to adjust for differences observed between the results of the organized screening laboratory and the other

laboratories before the introduction of LBC. Nevertheless, the study design cannot exclude that observed differences between the performance of LBC and that of conventional cytology could be due to differences in the underlying populations and in the proficiency of the cytologists reading the slides. [The Working Group noted a very high risk of bias in this study.]

Gradual implementation of LBC in Japan apparently led to a 2-fold higher detection rate of CIN2+ and CIN3+. (Akamatsu et al., 2012). However, the analysis did not take into account differences in age, previous history of screening, and calendar time, i.e. those factors that could influence detection, with only raw numbers of tests performed and lesions found reported. [The Working Group noted a very high risk of bias in this study.]

A comparison before and after implementation of LBC with computer-assisted reading in Denmark (Rebolj et al., 2015) found slightly different results for the FocalPoint/SurePath system compared with the ThinPrep Imaging System. In this analysis, the effect of the introduction of LBC cannot be distinguished from the effect of the introduction of computer-assisted technology. Although ThinPrep had similar detection rates compared with conventional cytology, SurePath identified more CIN2+ and CIN3+. However, PPV was improved by 50% with ThinPrep but was 14% lower with the SurePath system than with conventional cytology. Neighbouring areas that continued using conventional cytology throughout the study period showed no changes, suggesting that any changes observed in the areas where LBC with computer-assisted cytology had been introduced were due to the new technologies. [The Working Group noted a high risk of bias in this study.]

One of the largest published studies comparing LBC with conventional cytology used data from the national screening programme in the Netherlands. Rozemeijer et al. (2016) reported an adjusted relative recall, compared with conventional cytology, that was slightly lower for ThinPrep and slightly higher for SurePath. The detection of CIN2+ was almost identical for ThinPrep and conventional Pap testing, and it was slightly higher with SurePath, with no significant difference in PPV between the three tests. Because the study included more than 3 million conventional Pap tests, 1.6 million ThinPrep slides, and 1.3 million SurePath slides, it had power to give very precise estimates adjusted for age, socioeconomic status, region, and calendar time. Furthermore, the national screening programme in the Netherlands started in 1980s, but the study covered the period 2000–2011; thus, even if the conventional Pap test was mostly used until 2005, there is no risk that the first rounds of screening, when detection is expected to be much higher, could bias the results. [The Working Group noted a low risk of bias in this study.]

Finally, the most recent population-based evaluation compared conventional Pap testing with LBC (a mix of 3 million ThinPrep slides and 757 320 SurePath slides) in opportunistic screening and organized screening in Japan (Ito et al., 2020). The referral rate was higher with LBC, as was the detection of CIN2+, but the detection of CIN3+ was similar. The PPV of LBC for detection of CIN2+ was slightly higher than that of conventional cytology, whereas the PPVs for detection of CIN3+ were almost identical. Relative estimates were adjusted for age, calendar period, and region. [The Working Group noted a low risk of bias in this study.]

In conclusion, results about sensitivity from these large population-based studies are quite consistent with those of the RCTs and paired-sample studies assessing cross-sectional test accuracy, but data on lower specificity or PPVs have not been confirmed in all programmes. The difference between early studies and these large population-based comparisons may depend on a learning curve for LBC. Indeed, most of the

Table 4.16 Characteristics of observational studies to assess the effect of the introduction of liquid-based cytology on screening performance and effectiveness

Reference Country	No. of women	Study design	Setting	Age at entry (years)	LBC procedure	Type of comparison	Reported end-points	Long-term outcomes
Blanks & Kelly (2010) England	~2.5 million 102 laboratories, 13 643 abnormal tests	Before-and-after analysis of aggregated quality assurance data from screening laboratories	Organized screening	25–64	ThinPrep; SurePath	Before and after in laboratories that shifted from Conv. to LBC during 2005–2008	PPV	No
Akamatsu et al. (2012) Japan	LBC: 29 119 Conv.: 49 108	Results for 2 consecutive rounds of screening during the shift from conventional Pap testing to LBC	Organized screening	NR	SurePath	Round 1: LBC vs Conv. Round 2: Conv. then Conv. Conv. then LBC LBC then LBC	Detection at round 1 and at round 2	Yes; CIN2+, CIN3+, and cervical cancer detection at next round
Sigurdsson (2013) Iceland	42 654 LBC tests in 20 439 women 103 909 Pap tests in 61 574 women	Comparison of conventional and LBC results in 2007–2011. Data adjusted for differences in pre-existing clinics before the introduction of LBC (2000–2004)	Spontaneous and organized screening	20–69	ThinPrep	LBC-observed outcomes vs expected outcomes	Relative detection Relative referral Relative PPV	No
Rebolj et al. (2015) Denmark	Conv. always: before, 47 300; after, 53 979 Conv. then SurePath: before, 23 849; after, 62 644 Conv. then ThinPrep: before, 33 614; after, 74 522	Before-and-after study with concomitant control	Organized screening	23–59	ThinPrep + ThinPrep Imaging System SurePath + FocalPoint + HPV triage for ASC-US	Conv. vs ThinPrep Conv. vs SurePath Before and after in areas that shifted from Conv. manual reading with repeat cytology for ASC-US to LBC + computer-assisted reading 1 area did not change during the study period	Relative referral Relative detection Relative PPV	No

Table 4.16 (continued)

Reference Country	No. of women	Study design	Setting	Age at entry (years)	LBC procedure	Type of comparison	Reported end-points	Long-term outcomes
Rozemeijer et al. (2016, 2017) Netherlands	Conv.: 3 028 865 ThinPrep: 1 591 792 SurePath: 1 303 817	Concomitant comparison in cohort study; women may change the exposure over time	Organized screening	29–63	ThinPrep; SurePath	Conv. vs ThinPrep Conv. vs SurePath SurePath vs ThinPrep Comparison of baseline outcomes (relative detection and relative referral) Long-term outcome: incidence of cancers after negative screening test	Relative referral Relative detection Cumulative detection of cancers after negative test	Yes; cumulative incidence of cervical cancer
Ito et al. (2020) Japan	3 815 131 ThinPrep: 3 057 810 SurePath: 757 321	Concomitant comparison in cohort study; women may change the exposure over time	Spontaneous and organized screening	≥ 20	ThinPrep; SurePath	Conv. vs any LBC Poisson regression to compare adjusted detection of CIN2+ and CIN3+	Relative detection Relative referral Relative PPV	No

ASC-US, atypical squamous cells of undetermined significance; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; Conv., conventional cytology; LBC, liquid-based cytology; NR, not reported; PPV, positive predictive value.

Table 4.17 Results from observational studies on screening performance with liquid-based cytology compared with conventional cytology

Reference Country	No. of women	Referral for further assessment	Detection of CIN2+ and CIN3+	PPV
Blanks & Kelly (2010) England	~2.5 million 102 laboratories, 13 643 abnormal tests SurePath and ThinPrep	NA	NA	PPV for CIN3+: Before (Conv.): severe dysplasia, 75%; moderate, 37%; mild, 7% After (LBC): severe dysplasia, 79%; moderate, 37%; mild, 7% PPV for CIN2+: Before (Conv.): severe dysplasia, 88%; moderate, 70%; mild, 23% After (LBC): severe dysplasia, 90%; moderate, 72%; mild, 19%
Akamatsu et al. (2012) Japan	Conv.: 49 108 LBC: 29 119 SurePath and ThinPrep	NA	Conv.: CIN2+ ($n = 123$), 2.5/1000; CIN3+ ($n = 66$), 1.3/1000; cancer ($n = 5$), 0.10/1000 LBC: CIN2+ ($n = 167$), 5.7/1000; CIN3+ ($n = 110$), 3.8/1000; cancer ($n = 13$), 0.45/1000 RR LBC vs Conv.: CIN2+: 2.3 (95% CI, 1.8–2.9) CIN3+: 2.8 (95% CI, 2.1–3.9) Cancer: 4.4 (95% CI, 1.5–15.7)	NA
Sigurdsson (2013) Iceland	103 909 Pap tests in 61 574 women 42 654 LBC tests in 20 439 women	Observed/expected ratio for ASC-US+ cytology with LBC (expected computed according to cytology distribution before introduction of LBC): Women aged 20–39 yr: 1.27 (P that ratio is different from 1 < 0.001) Women aged 40–69 yr: 0.88 (P that ratio is different from 1 = 0.026)	Observed/expected ratio for CIN2+ with LBC (expected computed according to results before introduction of LBC): Women aged 20–39 yr: Observed/expected CIN2+: 1.06 (P that ratio is different from 1 = 0.36) Observed/expected CIN3+: 0.96 (P that ratio is different from 1 = 0.67) Women aged 40–69 yr: Observed/expected CIN2+: 0.75 (P that ratio is different from 1 = 0.82) Observed/expected CIN3+: 0.74 (P that ratio is different from 1 = 0.13)	PPV of ASC-US+ cytology for CIN2+: Women aged 20–39 yr: Conv.: 34.1% LBC: 34.8% Women aged 20–39 yr: Conv.: 16.1% LBC: 19.0%

Table 4.17 (continued)

Reference Country	No. of women	Referral for further assessment	Detection of CIN2+ and CIN3+	PPV
Rebolj et al. (2015) Denmark	Conv. always: before, 47 300; after, 53 979 Conv. then SurePath: before, 23 849; after, 62 644 Conv. then ThinPrep: before, 33 614; after: 74 522	Relative proportion of ASC-US+: Conv. always: 0.98 (95% CI, 0.91–1.07) SurePath vs Conv.: 1.99 (95% CI, 1.87–2.11) ThinPrep vs Conv.: 0.70 (95% CI, 0.66–0.75)	Relative before/after detection of CIN2+: Conv. always: 1.02 (95% CI, 0.88–1.18) SurePath vs Conv.: 1.71 (95% CI, 1.53–1.91) ThinPrep vs Conv.: 1.06 (95% CI, 0.93–1.21) Relative before/after detection of CIN3+: Conv. always: 1.10 (95% CI, 0.93–1.30) SurePath vs Conv.: 1.66 (95% CI, 1.46–1.88) ThinPrep vs Conv.: 0.99 (95% CI, 0.85–1.15)	Relative before/after PPV of ASC-US cytology for CIN2+: Conv. always: 1.03 (95% CI, 0.92–1.16) SurePath vs Conv.: 0.86 (95% CI, 0.79–0.94) ThinPrep vs Conv.: 1.51 (95% CI, 1.36–1.68) Relative before/after PPV of ASC-US cytology for CIN3+: Conv. always: 1.12 (95% CI, 0.97–1.29) SurePath vs Conv.: 0.83 (95% CI, 0.75–0.93) ThinPrep vs Conv.: 1.41 (95% CI, 1.23–1.61)
Rozemeijer et al. (2016, 2017) Denmark	Conv.: 3 028 865 ThinPrep: 1 591 792 SurePath: 1 303 817	OR of cytology ≥ borderline or mild dyskaryosis: ThinPrep vs Conv.: 0.96 (95% CI, 0.93–0.99) SurePath vs Conv.: 1.12 (95% CI, 1.09–1.16)	OR of cytology having a CIN2+ detected: ThinPrep vs Conv.: 0.99 (95% CI, 0.96–1.02) SurePath vs Conv.: 1.08 (95% CI, 1.05–1.12)	OR: PPV of cytology ≥ borderline or mild dyskaryosis for histology: ThinPrep vs Conv.: CIN2: 1.08 (95% CI, 0.99–1.17) CIN3: 1.06 (95% CI, 0.99–1.13) Cancer: 0.98 (95% CI, 0.83–1.15) SurePath vs Conv.: CIN2: 1.06 (95% CI, 0.98–1.15) CIN3: 0.97 (95% CI, 0.91–1.03) Cancer: 0.94 (95% CI, 0.80–1.10)
Ito et al. (2020) Japan	ThinPrep: 3 057 810 SurePath: 757 321	Conv.: 1.13% (34 435) LBC: 1.49% (11 443) Crude RR, 1.32 (95% CI, 1.30–1.35)	Adjusted RR, LBC vs Conv.: CIN2+: 1.16 (95% CI, 1.08–1.25) CIN3+: 1.00 (95% CI, 0.90–1.11)	Adjusted RR, LBC vs Conv.: CIN2+: 1.17 (95% CI, 1.09–1.26) CIN3+: 1.01 (95% CI, 0.91–1.12)

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; LBC, liquid-based cytology; NA, not applicable; OR, odds ratio; PPV, positive predictive value; RR, relative risk; yr, year or years.

initial studies were conducted by cytologists whose university education had been based on conventional cytology and who were retrained to LBC, whereas these large population-based studies also included cytologists who have had more experience with LBC in their routine work; some cytologists even started their professional activity using LBC. It is not possible to determine whether the new generation of cytologists, who began their studies and training with LBC in the USA and, more recently, in many countries in Europe and Asia, would produce different values of relative sensitivity and, particularly, of specificity.

(d) Evidence on the effectiveness of LBC in routine cervical screening programmes

The aim of cervical cancer screening is to prevent cancer incidence through the detection and treatment of CIN2+ lesions. However, there is evidence that only 30% of CIN3 lesions progress to cancer in a 30-year time span (McCredie et al., 2008), and this proportion is even lower for CIN2 lesions. Most CIN2 lesions, and also CIN3 lesions, will regress spontaneously (Ronco et al., 2008) or persist without progression. Therefore, an increase in CIN2+ detection is an advantage only if it includes those lesions that would progress to cancer or at least would persist for a long time. To test the efficacy of LBC with this longitudinal approach, it is necessary to conduct studies with a long-term follow-up of women who tested negative in one of the two tests and to observe the cumulative incidence of cancer or CIN3 as a surrogate of cancer risk. This is not possible with paired-sample studies, because in these studies women are managed (i.e. assessed and eventually treated) according to the results of both tests. Only RCTs with long-term outcome assessment and concurrent cohort studies can provide a longitudinal approach.

One RCT (Strander et al., 2007) and two observational studies (Akamatsu et al., 2012; Rozemeijer et al., 2017) have published results

comparing the cumulative incidence of CIN or cervical cancer after a negative test result from LBC or conventional cytology screening (Table 4.18).

The RCT in Sweden (Strander et al., 2007) reported a cumulative incidence from 1.5 years after recruitment up to 3 years and 7 months (i.e. excluding lesions found at recruitment, but including those found at the next screening round) of 6 per 1000 for LBC and 5.3 per 1000 for conventional cytology (RR, 1.12; 95% CI, 0.68–1.83). [The Working Group noted a low risk of bias and a very imprecise estimate in this study.]

Akamatsu et al. (2012), in Japan, reported a lower detection of CIN2+, CIN3+, and invasive cancer after LBC (SurePath); the numbers were small, however, and the difference may have been due to chance. Furthermore, the populations screened with LBC and conventional cytology were not comparable, but the authors could not adjust for possible confounders. [The Working Group noted a very high risk of bias in this study.]

Finally, the largest study compared the cumulative incidence of invasive cancer after conventional cytology and two different LBC systems (ThinPrep and SurePath) in the national screening programme in the Netherlands (Rozemeijer et al., 2017). The authors adjusted the estimates for age, socioeconomic status, calendar period, and region and found very similar incidence rates of cancer detected by LBC and conventional cytology (Table 4.18); SurePath showed a significant reduction in cancer incidence compared with both conventional cytology and ThinPrep. [The Working Group noted a low risk of bias in this study.] A previous study in the Netherlands comparing two smaller cohorts from the national screening programme, one screened with conventional cytology and one with LBC, found a 50% lower occurrence of CIN2+ in a follow-up of about 1.5 years after a negative LBC test result compared with conventional cytology (7 of 34 219 vs 21 of 49 856; P = 0.091) (Beerman

et al., 2009); some of the women included in this study may be also included in the study of Rozemeijer et al. (2017).

4.3.4 Cytology based on Romanowsky–Giemsa staining

(a) Definition of Romanowsky–Giemsa staining

The term "Romanowsky–Giemsa staining" or "Romanowsky staining" refers to several techniques used to stain cytological specimens, in which the Romanowsky effect is used to differentiate the cell components through different colour hues (Theil, 2012; Bezrukov, 2017), in particular the purple staining of chromatin. Nuclei stained with these techniques show variations in staining that enable characterization of their morphology. The technique is named after Romanowsky (Krafts & Pambuccian, 2011). The effect is based on the use of two dyes, eosin and a methylene blue that has been subject to oxidative demethylation. This dye, called polychrome methylene blue, is a mix of several molecules, including methylene blue, azure A, azure B, azure C, thionine, methylene violet Bernthsen, methyl thionoline, and thionoline (Marshall, 1978).

Techniques based on the Romanowsky effect have been used for a long time to stain many types of cytological specimens, and are still the standard for the diagnosis of infection with *Leishmania* and other disease-causing microorganisms, such as *Plasmodium* (malaria), *Toxoplasma*, and *Pneumocystis* (Marshall, 1978; Horobin, 2011; Li et al., 2012; Bain, 2017). The technique is also still used to stain haematological smears (Horobin, 2011; Theil, 2012; Bain, 2017).

For gynaecological cytology, the technique has been completely replaced by Pap staining (Spriggs, 1977; Broder, 1992; Solomon et al., 2002) except for in some countries of the former Soviet Union.

(b) Differences between Romanowsky–Giemsa staining and Pap staining

Romanowsky–Giemsa staining was developed for air-dried specimens, whereas the Pap stain is used for wet-fixed specimens. Wet fixation enables better differentiation of nuclear chromatin structures, particularly nucleoli, and better characterization of nuclear shape abnormalities that are present in neoplastic cells (Krafts & Pambuccian, 2011). Another limitation of the Romanowsky–Giemsa stain compared with the Pap stain is its inability to characterize cytoplasmic keratinization, a feature that is particularly important in the diagnosis of squamous cell neoplasia (Krafts & Pambuccian, 2011). Finally, the Romanowsky–Giemsa stain does not penetrate well into the small, three-dimensional groups of cells that may be present in cytological specimens; this results in an absence of staining in inner cells. In contrast, the Pap stain method can stain small groups of overlapping cells (Krafts & Pambuccian, 2011).

The Romanowsky–Giemsa stain also has advantages. For example, in air-dried specimens the differences between the nuclear and cytoplasmic diameters are magnified, which is useful in distinguishing potential cellular transformation (Boon & Tabbers-Bouwmeester, 1980; Boon & Drijver, 1986). Chromatin is hyperchromatic, which enables a better impression at low magnification, but there is reduced detail of the nuclear structures at higher magnifications. Some cytoplasmic structures are better defined, and chondroid cytoplasmic material can be identified (Krafts & Pambuccian, 2011). Also, a Leishman–Giemsa cocktail, which is based on two staining solutions, both of which produce the Romanowsky effect, enables better staining of nuclei, on the basis of chromatin, vesicularity, and membrane integrity, and higher quality of cytoplasm staining, on the basis of the transparency and nature of the cell membrane, compared with Pap staining (Padma et al., 2018).

Table 4.18 Long-term outcomes of cervical cancer screening by liquid-based cytology compared with conventional cytology

Reference Country	Design	No. of women	Detection	IRR or RR
Strander et al. (2007) Sweden	RCT with 3 yr and 7 mo follow-up	Conv.: 8810 LBC: 4674	CIN2+ detection during follow-up from 1.5 yr to 3 yr and 7 mo after recruitment, all screened as routine: After LBC: 0.60% (28/4674) After Conv.: 0.53% (47/8810)	RR, 1.12 (95% CI, 0.68–1.83)
Akamatsu et al. (2012) Japan	Results for 2 consecutive rounds of screening during the shift from conventional Pap testing to LBC	Conv. then Conv.: 73 253 Conv. then LBC: 33 318 LBC then LBC: 51 723	Conv. then Conv.: CIN2+ (n = 115), 1.6/1000; CIN3+ (n = 58), 0.8/1000; cancer (n = 10), 0.14/1000 Conv. then LBC: CIN2+ (n = 38), 1.1/1000; CIN3+ (n = 24), 0.7/1000; cancer (n = 2), 0.06/1000 LBC then LBC: CIN2+ (n = 41), 0.8/1000; CIN3+ (n = 24), 0.5/1000; cancer (n = 1), 0.02/1000	LBC then LBC vs Conv. then LBC: CIN2+: RR, 0.70 (95% CI, 0.44–1.11) CIN3+: RR, 0.64 (95% CI, 035–1.18) Cancer: RR, 0.32 (95% CI, 0.01–6.19)
Rozemeijer et al. (2017) Netherlands	Concomitant comparison in cohort study; women may change the exposure over time	Conv.: 3 028 865 ThinPrep: 1 591 792 SurePath: 1 303 817	72 mo cumulative incidence of cervical cancer after normal cytology: Conv.: 1042 cancers; 13 796 018 person-yr ThinPrep: 328 cancers; 5 201 188 person-yr SurePath: 231 cancers; 4 835 917 person-yr	Adjusted IRR, SurePath vs Conv., 0.81 (95% CI, 0.66–0.99) Adjusted IRR, ThinPrep vs Conv., 1.15 (95% CI, 0.95–1.38)

CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; Conv., conventional cytology; IRR, incidence rate ratio; LBC, liquid-based cytology; mo, month or months; NA, not applicable; PPV, positive predictive value; RCT, randomized controlled trial; RR, relative risk; yr, year or years.

Finally, the main advantage of the Romanowsky–Giemsa stain is that the procedure for preparing the slides is less time-consuming and uses reagents that are less expensive and easier to obtain (Jarynowski, 2019).

(c) Use of the technology

Romanowsky–Giemsa staining is used for gynaecological cytology in countries of the former Soviet Union, where it is described mostly with the following names: Romanowsky–Giemsa, May–Grünwald–Giemsa, and Pappenheim (Rogovskaya et al., 2013).

The first official document describing the application of the Romanowsky–Giemsa stain for cervical specimens was published in 1976 when Order No. 1253 was issued by the Ministry of Health of the Soviet Union. With almost no changes, the method was used until the dissolution of the Soviet Union and the emergence of the newly independent states. Table 4.19 lists documents stating recommendations for the use of Romanowsky–Giemsa staining in cervical cancer screening in the countries of the former Soviet Union.

There are few reports on the change in cervical cancer screening methods in countries of the former Soviet Union. Three Baltic countries – Estonia, Latvia, and Lithuania – became part of the European Union and implemented Pap-based cervical cancer screening programmes in 2004–2006. In Belarus, Pappenheim staining (a modification of Romanowsky–Giemsa staining) is used (IARC, 2012). In Kazakhstan, services successfully moved to Pap-based screening in 2008 (Aimagambetova & Azizan, 2018; Bekmukhambetov et al., 2018). In the Republic of Moldova, a shift to Pap testing started after 2016, but barriers related to cost and training have been described (Davies et al., 2016; Jarynowski, 2019). Analysis of cervical screening services in the Republic of Moldova by an external adviser for the ministry of health also pointed out that the absence of an international community for standardization makes quality improvement difficult (Davies et al., 2016).

In the Russian Federation, where cervical screening is budgeted by region, some countries have changed to Pap testing. Since 2019, the Ministry of Health of the Russian Federation has recommended against the use of Romanowsky–Giemsa staining for cervical screening (see Table 4.19). Implementation of this recommendation was affected by several barriers, including the higher costs of the reagents and the need for complete retraining of cytotechnicians and cytologists. In Ukraine, there is no clear document recommending a shift from cytology based on Romanowsky–Giemsa staining to Pap testing, mostly because of economic barriers to the implementation of Pap testing.

In other countries in central Asia, the situation is unclear. In 2017, the United Nations Population Fund (UNFPA) funded a project on the use of VIA in Tajikistan (UNFPA, 2019), which suggested that infrastructure for cytology was not sufficient. In Turkmenistan, Pap staining followed by retesting with Romanowsky–Giemsa, or HPV testing, is replacing the use of cytology based on Romanowsky–Giemsa staining as a stand-alone technique because of an improvement in economic resources compared with other countries in central Asia; however, the coverage is probably low (Rogovskaya et al., 2013).

(d) Epidemiology of cervical cancer in countries in eastern Europe and central Asia

WHO data on cervical cancer mortality from 1975 to 2005 show a different trend in most eastern European countries compared with western European countries (La Vecchia et al., 2010). In general, most western European countries had a decreasing trend, whereas in eastern European countries mortality rates were essentially stable or had a slight increasing trend (see also Section 1.1.1, Fig. 1.5), with the exception of

Table 4.19 Former and current use of cytology based on Romanowsky-Giemsa staining

Country	Position of official guidelines	Use of technology	References
Belarus	NA	Pappenheim staining observed during the IARC visit to the National Cancer Centre in Minsk in February 2019 for the IARC-WHO Regional Office for Europe training course	IARC (2012)
Kazakhstan	NA	Mainly opportunistic screening by cytology based on Romanowsky–Giemsa staining until 2007. From 2008, 60% of all smears were prepared using the Pap stain and 40% using the Romanowsky–Giemsa stain. Since 2009, 100% of screening smears use Pap staining	Aimagambetova & Azizan (2018)
Republic of Moldova	Recommendation to progressively change from Romanowsky–Giemsa staining to Pap staining during the course of 2017	Opportunistic screening, with the majority using Romanowsky–Giemsa staining	Davies et al. (2016)
Russian Federation	Order No. 124 (13 March 2019): Pap testing only. This effectively cancelled the previous Order No. 869 (26 October 2017), when Romanowsky–Giemsa staining was officially mentioned	Cervical smear test with Romanowsky–Giemsa or May–Grünwald–Giemsa staining. Until 2017, annual examinations for women aged ≥ 18 yr or after first intercourse, with no upper age limit. Moscow used a screening age range of 35–69 yr and a screening interval of 3 yr Officially, it should now be Pap testing only. However, some centres still use Romanowsky–Giemsa staining because it is less expensive. [The regions are responsible for budgets.]	Olson et al. (2016); Ministry of Health of the Russian Federation (2019)
Soviet Union	Order No. 1253 (30 December 1976) introduced the use of Romanowsky–Giemsa staining across the whole country	In 1964, annual cytology screening was introduced in the former Soviet Union as part of routine cervical cancer screening; in 1976, the Ministry of Health of the Soviet Union established centralized cytology laboratories in all regions and republics. Opportunistic basis, using Romanowsky–Giemsa staining or haematoxylin and eosin staining	Rogovskaya et al. (2013); Olson et al. (2016)
Turkmenistan	Order No. 144 (2014)	Pap testing followed by Romanowsky–Giemsa staining or HPV testing	WHO (2019)

HPV, human papillomavirus; NA, not available; yr, year or years.

Czechia, where data are available only since 1987 and there has been a slight decrease.

More detailed analyses from the Russian Federation (Barchuk et al., 2018) showed a slight decline in cervical cancer mortality rates until the early 1990s, followed by a slight increase after the mid-1990s. An increasing trend in incidence rates has been observed since 1989, when data are available for the Russian Federation (Barchuk et al., 2018), and from other countries in eastern Europe and central Asia (Bruni et al., 2019a, b). A detailed analysis from the Arkhangelsk Regional Cancer Registry in the north-west of the Russian Federation (Grjibovski et al., 2018) found that both incidence and mortality rates increased from 2000 to 2014 but incidence increased more than mortality, showing that survival for women with cervical cancer had improved, possibly because of earlier detection and management; consistent with this, incident cancers showed a simultaneous shift to earlier stages at diagnosis. These figures suggest two conflicting effects: an increased risk of occurrence and an improvement in the early diagnosis of cancers. It is impossible to tell whether this improvement in early diagnosis also affected incidence through detection and treatment of precancerous lesions, but if an effect is present it is not sufficiently strong to reverse the increase in risk, probably as a result of an increase in HPV prevalence.

Countries in eastern Europe and central Asia have the highest incidence of cervical cancer in Europe, independent of the screening test coverage that they reported (Ferlay et al., 2018; Bruni et al., 2019a, b; Arbyn et al., 2020).

(e) Evidence on accuracy and effectiveness

(i) Accuracy

Limited data were found comparing the diagnostic accuracy of Romanowsky–Giemsa staining and the Pap test. Romanowsky–Giemsa staining (90%) has a lower specificity than the Pap test (98%) to distinguish cervical precancer;

this is usually mitigated by repeating the test to reduce the possibility of missing women with precancer (Davies et al., 2016; Jarynowski, 2019). No data were available on sensitivity and on how it may be affected by repeating tests to increase specificity.

(ii) Performance in screening programmes

Table 4.20 summarizes the data on the performance of Romanowsky–Giemsa staining in screening programmes that are available in the peer-reviewed and grey literature.

Data on performance can provide some information about or insights into the accuracy of the programme, taking into consideration that the first-level test is usually the main determinant of programme accuracy, but it is not the only one. Furthermore, performance indicators are strongly influenced by the quality of routinely collected data, particularly the detection rate, because missing even a few lesions may lead to a large underestimation of the indicator. The few documents reporting the proportion of unsatisfactory samples when using Romanowsky–Giemsa staining show values that are close to or higher than the upper bound of the range observed in western European countries with Pap staining, i.e. about 10%. When data from different laboratories enable benchmarking (Davies et al., 2016), the proportion of unsatisfactory slides varies widely (ranging from 0% to 5.7%), which suggests low reproducibility of the technique. [This heterogeneity may come from differences in the way in which cytologists from different laboratories interpret the findings or from variability in how samples are collected and processed.] A high variability between laboratories in the detection rates of LSIL and HSIL was also reported.

The detection rate varies widely. [It is not clear whether the available data report histologically confirmed cases or simply the cytological classification (which would be not a detection rate but a proportional analysis of positives).] In

some cases (Iskhakova et al., 2012; Table 4.20), the detection rate is very low compared with the cervical cancer incidence in the region; [this suggests that the programme has poor sensitivity or that there is underreporting of histological findings].

Data on referral rates were not identified. [It is not clear how women with abnormal findings are managed, i.e. whether with direct referral for colposcopy or with repeated cytology.] Consequently, no data on PPV were found or could be estimated from the available reports.

(iii) Efficacy and effectiveness

No trials have been identified that compare the efficacy of cytology based on Romanowsky–Giemsa staining with that of Pap testing or other cytological staining techniques.

No controlled studies on the effect of screening programmes on cervical cancer incidence or mortality have been identified.

Time-trend studies conducted after the dissolution of the Soviet Union in 1989, as well as data from routine cancer statistics, showed no reduction and in some cases an increase in cervical cancer incidence and mortality rates in most of the countries where Romanowsky–Giemsa staining is used for screening (La Vecchia et al., 2010; Barchuk et al., 2018; Grjibovski et al., 2018; Bruni et al., 2019a, b). This trend is common to almost all countries in eastern Europe and central Asia, except Czechia, independent of the method of cytology staining used and of the reported coverage of the screening test (La Vecchia et al., 2010; Bruni et al., 2019a, b).

4.3.5 Harms of cytological techniques

(a) Physical harms

Pelvic examination is a very sensitive medical procedure, and special considerations are needed. Bloomfield et al. (2014) performed a systematic review of pelvic examination in asymptomatic, non-pregnant, average-risk adult women. Eight studies including 4576 women reported that women experienced pain or discomfort; the median rate was 35%, and rates ranged from 11% to 60%. Rates of fear, embarrassment, or anxiety ranged from 10% to 80%. Pain can be exacerbated by atrophic vaginal mucosa and vaginal dryness in menopausal women (Elit, 2014). However, some studies conducted in the United Kingdom reported that younger women experience more embarrassment and pain than older women (Yu & Rymer, 1998; Fiddes et al., 2003).

Although female patients usually prefer a female physician for gynaecological examinations, one study in 167 women with median age 25 years in the USA found that pain scores for examinations by male physicians and female physicians were not significantly different (Moettus et al., 1999).

In a cross-sectional study reporting on the pain and physical discomfort experienced during a Pap test, Hoyo et al. (2005) carried out a questionnaire survey of 144 African American women aged 45–65 years. They reported that 45.8% of women who did not attend screening and 17.5% of women who attended screening experienced pain during the cytological examination ($P < 0.0001$). Women who felt pain during the cytological examination were less likely to participate in further cervical cancer screening. In a study in Vietnamese American women aged 18–64 years, 55% of 240 women who had had cytology within 3 years reported that concern about pain or discomfort was a barrier to cytological examination (OR, 0.5; 95% CI, 0.3–1.1) (Taylor et al., 2004). In a longitudinal cohort study in 490 sexually active young women aged 12–24 years who presented to a hospital-based adolescent clinic in the USA, Kahn et al. (2003) reported that women who returned for a follow-up visit were more likely to believe that the follow-up Pap test would not be painful compared with those who did not return (77% vs 65%, OR, 1.73; 95% CI, 1.08–2.83).

Table 4.20 Performance and detection rate of precancerous lesions using Romanowsky–Giemsa staining

Reference	Country Date	Setting	Population/no. of tests (N)	Unsatisfactory samples	Detection rate (%)
Iskhakova et al. (2012)	Russian Federation 2009–2011	Meleuz (Bashkortostan), centralized cytological laboratory	79 710 women, aged 20–60 yr	Unsatisfactory: 0.6% Insufficiently satisfactory: 15.6% Satisfactory: 80.3%	CIN1: 0.3 ($n = 168$) CIN2: 0.2 ($n = 86$) CIN3: 0.05 ($n = 43$) CIS: 0.02 ($n = 13$) Cervical cancer: 0.02 ($n = 13$)
Kozyreva et al. (2012)	Russian Federation	Vladikavkaz (North Ossetia), oncological dispensary	9525 nuclei of malignant and normal cervical cells	NR	Number detected (%): CIN1: 530 (0.056%) CIN2: 960 (0.100%) CIN3: 890 (0.093%)
Chernyakova (2016)	Ukraine 2015	Kharkiv, university clinic	37 women aged 20–64 yr enrolled in "opportunistic screening"	19 women – inflammation; *Chlamydia* in 9.6%, HPV in 28.5% CIN1 in 2/37 Cytology–colposcopy discrepancy in 5/37	NR
Davies et al. (2016)	Republic of Moldova 2015	National audit Data from 7 of the largest laboratories	236 579 smears	Between laboratories, proportion of abnormal results varied from 0.32% to 6.06%, and unsatisfactory results varied from 0.0% to 5.7%	Range between laboratories: ASC-US: 0.04–0.64 LSIL: 0.02–2.35 HSIL: 0.02–2.10 AGUS: 0.0–0.01 ASC-H: 0.0–0.26 Cervical cancer: 0.0–0.18
Aktanko et al. (2018)	Russian Federation	Vladivostok	4032 women, aged > 25 yr	NR	CIN1: 21.9 ($n = 20$) CIN2: 12.1 ($n = 11$) CIN3: 19.7 ($n = 18$) CIS: 4.4 ($n = 4$) SCC: 30.7 ($n = 28$) Adenocarcinoma: 1.09 ($n = 1$)
Grebenkina et al. (2018)	Russian Federation 2018	Nizhny Novgorod, reference cytological centre; evaluated 10% of all cytological and 100% of all indeterminate samples	9415 cytological smears 12% processed by Romanowsky–Giemsa	23% of all slides (not only Romanowsky–Giemsa stained smears)	21–36% did not match the final diagnosis (including 2 missed cervical cancers)

Table 4.20   (continued)

Reference	Country Date	Setting	Population/no. of tests (N)	Unsatisfactory samples	Detection rate (%)
Kirillina et al. (2018)	Russian Federation 2017	Yakutia, different women's clinics	7600 women, aged 18–88 yr	Non-informative material: 1.9% Glandular epithelium not taken: 19.4%	All CIN+: 4.7 ($n = 359$) CIN1: 61.3 ($n = 220$) CIN2: 24.5 ($n = 84$) CIN3: 10.6 ($n = 38$) CIS + cervical cancer: 1.1 ($n = 4$, cervical cancer = 2)

AGUS, atypical glandular cells of undetermined significance; ASC-H, atypical squamous cells cannot exclude high-grade; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions; NR, not reported; SCC, squamous cell carcinoma; yr, year or years.

When stirrups are used during the pelvic examination and cervical sampling, women are compelled to be in the dorsal lithotomy position, which can cause discomfort. Seehusen et al. (2006) measured physical and psychological effects in an RCT of 197 women who underwent gynaecological examinations in the USA with stirrups ($n = 97$) or without stirrups (women were examined with their feet placed on the corners of a fully deployed table extension; $n = 100$). All the women were draped with a full-sized sheet in a standardized manner that maximized the coverage of the body and enabled visualization of the perineum. Physical discomfort was higher in women who were examined with stirrups compared with those examined without stirrups (30.4% vs 17.2%). There was no significant reduction in sense of loss of control.

Korfage et al. (2012) sent questionnaires to the home addresses of 789 screening participants in the Netherlands before screening, after screening, and again with the screening results, to assess the effect of cervical cancer screening on health-related quality of life in women with normal test results. A female age-matched reference group ($n = 567$) was included. Although the average age was not significantly different between the groups (45.3 years vs 45.8 years; $P = 0.29$), the proportion of postmenopausal women was unknown. About 40% of screening participants experienced at least one of the following symptoms at least 1 day after the smear had been taken: lower abdominal pain, vaginal bleeding, discharge, urinary problems, or feeling sick. These symptoms were very painful or fairly painful for 12% of women.

(b) Psychological harms

Psychological harms can be experienced: (i) when samples are collected, (ii) as a result of waiting time to receive the results, (iii) from unsatisfactory smears, (iv) from abnormal results, and (v) upon follow-up because of abnormal results. All women in whom smears are taken have the potential to experience the first kind of harm. The potential effect of the second kind of harm will vary depending on the woman's previous knowledge and experience of cervical cancer screening. Other harms are limited to women with unsatisfactory and abnormal test results.

(i) All participants

Women naturally feel some personal embarrassment and discomfort when smears are taken for cervical cancer screening, as described above. In the Netherlands, Korfage et al. (2012) assessed the effect of cervical cancer screening on health-related quality of life in 789 women with normal test results, compared with a reference group ($n = 563$). Screening-specific anxiety was lower in the screened women than in women who had not been screened. When results before and after screening were compared, the EQ-5D rating of own health increased, the mental health score (Mental Component of the Short-Form 12) increased, and the general anxiety score (Spielberger State-Trait Anxiety Inventory [STAI-6]) decreased. There were no differences between the results in younger and older women. Although 19% reported a feeling of shame, pain, inconvenience, and nervousness during the smear-taking procedure, 80% of women were satisfied with their results after the cytology procedure.

In an interview survey in 13 women of various ages and backgrounds by Larsen et al. (1997), nearly all the women who had pelvic examination indicated that they were nervous before the consultation, but they regarded the examination as a necessary procedure for diagnosis. The women identified several factors that affected their ability to feel in control during the procedure, such as the physician's gender, informed communication, positioning during the examination, a feeling of lost integrity while naked, and trust in the physician. Yanikkerem et al. (2009) also emphasized the necessity of providing information during the gynaecological examination,

based on a questionnaire survey of 433 women who attended a gynaecological outpatient clinic in Turkey. In an interview survey of 262 women aged 21–65 years by Norrell et al. (2017), 62% of participants believed that open communication with their health-care provider was helpful in understanding the purpose and value of a pelvic examination. In further cohort studies in the USA and Europe, good communication positively affected the screening experience and improved screening adherence (Taylor et al., 2004; Thangarajah et al., 2016; Freijomil-Vázquez et al., 2019).

(ii) Women waiting to receive cytology results

Freijomil-Vázquez et al. (2019) carried out an interview survey of 21 women aged 21–52 years with confirmed diagnosis of CIN recruited from a gynaecology clinic in Spain. When health-care providers gave limited information about diagnosis, the women's anxiety increased as a result of the uncertainty and lack of decision-making ability they felt about the prevention and treatment of CIN.

In a questionnaire survey by Korfage et al. (2012), general anxiety and screen-specific anxiety levels were compared before and after Pap tests in 789 women in the Netherlands. A female age-matched reference group including 567 randomly selected women (aged 30–70 years) who were not due for cervical cancer screening within the next 2 years were sent a questionnaire through the regional screening organization in Maastricht. Screening participants reported less screen-specific anxiety ($P < 0.001$) than the reference group before screening, after screening, and also after the receipt of test results. After a normal result was received, general anxiety, as judged by the STAI-6, decreased slightly. Screen-specific anxiety measured using the Psychological Consequences Questionnaire increased initially but then decreased after the receipt of the Pap test results.

(iii) Women with unsatisfactory test results

The rates of unsatisfactory test results differ between screening programmes (see Section 4.3.1), and women with unsatisfactory test results can have higher levels of anxiety compared with women with normal test results. French et al. (2004) studied the psychological effects in 180 women with unsatisfactory smears and 226 women with normal results in the United Kingdom. Women with unsatisfactory test results had higher scores for state anxiety (STAI-6) and concern about the test results, perceived themselves to be at a higher risk of cervical cancer, and were less satisfied with the information they received about their test result compared with women with normal test results.

(iv) Women with abnormal test results

Most studies that reported the anxiety experienced by women after receiving an abnormal cytology test result were cross-sectional questionnaire surveys. Some studies investigated the duration of the psychological effects after receiving an abnormal test result.

Maissi et al. (2004) performed a questionnaire survey and compared the psychological effects in 366 women with normal results and 1010 women with abnormal test results (borderline or mild dyskaryosis) in the United Kingdom. Women with normal results had significantly lower scores for state anxiety (STAI-6), emotional distress (12-item General Health Questionnaire [GHQ-12]), and concern about test results than those with abnormal results. Similar findings were reported by Wardle et al. (1995), also in the United Kingdom.

A study in Sweden reported the results of a questionnaire survey of 242 women with two consecutive Pap tests reported as mild dysplasia (CIN1) who should, as a consequence, have undergone colposcopy and biopsy according to an agreed general programme (Ideström et al., 2003). Most women were satisfied with the follow-up; 72% felt they understood the meaning

and consequences of having mild dysplasia. Nevertheless, 59% reported feeling worried and anxious. Moreover, 30% of women thought that the results affected their daily life because of the stress induced by the need for additional testing, and 8% reported a negative influence on sexuality and their experience of sexual intercourse as a consequence of the management of mild dysplasia.

In the Trial of Management of Borderline and Other Low-grade Abnormal smears (TOMBOLA) study conducted in the United Kingdom, Gray et al. (2006) performed a questionnaire survey of the psychological and psychosocial effects in 3671 women with a low-grade abnormality (borderline nuclear abnormalities or mild dyskaryosis). On the Hospital Anxiety and Depression Scale (HADS), 57% of women had no anxiety (a score of < 8 is defined as a cut-off point for anxiety by the HADS anxiety subscale), 20% had scores consistent with some level of anxiety (scored 8–10), and 23% had scores that indicated a probable clinically significant level of anxiety (scored ≥ 11). Most women (91%) were classed as non-cases on the depression subscale (a score of < 8 is defined as a cut-off point for no depression by the HADS depression subscale). Statistically significant associations were found between reported anxiety and younger age, increased physical activity, ever having had a child, and current smoking status. There was also a strong association between anxiety and depression scores: 95% of women who scored ≥ 8 on the depression subscale also scored ≥ 8 on the anxiety subscale. In a multivariate analysis, significant associations were found between anxiety and worries about general health, feelings about self, worries about cervical cancer, future fertility, sex life, perceived risk of cervical cancer, and support received.

Pirotta et al. (2009) assessed the psychological effects of an abnormal Pap test result in 333 women aged 18–45 years in Australia who completed a survey 3 months after receiving their test results. General health-related quality of life scores were assessed using the EuroQol Visual Analogue Scale, in which participants select their current health status on a scale from 0 (death) to 100 (perfect health). The results were nearly equal in women with a normal smear, women with an abnormal smear, and women with confirmed CIN. The scores for worries and concerns, emotional impact, and control using the Human Papillomavirus Impact Profile were higher in women with abnormal Pap tests and CIN than in women with normal Pap tests. Concerns about effects on sex life and self-image were observed in women with high-grade lesions or external genital warts, but not in those with low-grade lesions.

Korfage et al. (2010) sent questionnaires to 270 women with borderline or mild dyskaryosis (BMD) test results in the previous 6–24 months identified through a regional screening organization, to evaluate general quality of life, general anxiety, and screen-specific anxiety. A similar questionnaire was sent to 372 randomly selected women (aged 30–60 years) who were due for screening (reference group). The women in the BMD group were younger than the women in the reference group (mean age, 43 years vs 46 years; $P < 0.001$); the proportion of postmenopausal women was unknown. Women in the BMD group had higher levels of general anxiety and screen-specific anxiety than those in the reference group; 44% of the BMD group had high anxiety (indicated by an STAI-6 score > 44) compared with 33% in the reference group ($P < 0.001$). This finding remained significant after adjustment for differences in age, job and marital status, having children or not, and country of birth. Although both groups reported positive attitudes towards the cervical cancer screening programme, women in the BMD group were more likely to report fear of cervical cancer as their reason for having a repeat smear taken, compared with women in the reference group (23% vs 4%; $P < 0.001$).

A questionnaire-based study in Germany to assess the psychological effect of an abnormal test result invited 595 women who had been referred to a special outpatient clinic with CIN for further evaluation (Thangarajah et al., 2016). Most of the women (68.8%) reported that they felt anxious on receipt of the test result, 26.3% felt panic, and 18.6% did not understand what the test result meant. After speaking with their physicians, 54.4% of women remained worried, 24.4% felt reassured, and 20.2% felt confident.

In an RCT in Norway, women were randomized to either hrHPV testing every 5 years (followed by cytology if hrHPV-positive; $n = 487$) or cytology testing every 3 years (followed by hrHPV testing if low-grade cytology was detected; $n = 521$); anxiety and depression scores were compared by screening group and by test result (Andreassen et al., 2019). The mean age was 51 years and was similar in both study groups. The frequency of abnormal primary cytology results ($\geq$ ASC-US) was 54% and of positive primary hrHPV test results was 53%. Compared with women who were screened with cytology, women screening with hrHPV were not more likely to experience mild anxiety and depression scores (RR, 0.96; 95% CI, 0.70–1.31) or more likely to experience moderate or severe anxiety and depression (RR, 1.14; 95% CI, 0.65–2.02). Similar findings were observed when analysis was restricted to women with abnormal cytology or positive hrHPV test results. The likelihood of having abnormal long-term anxiety or depression scores for 4–24 months after screening in women aged 34 years and older was not affected by the screening method or the screening results.

Although anxiety and distress associated with screening and diagnosis have been reported, findings differed in studies because of sociodemographic, behavioural, and age differences in women included in these studies. In a qualitative study in Denmark examining the experiences of women with different stages of cervical dysplasia and whether their knowledge of HPV as the cause of cervical dysplasia influenced their perception of their disease, Lee Mortensen & Adeler (2010) conducted a focus group interview of 12 women with different stages of cervical dysplasia. The participants considered cervical dysplasia to be a highly distressing condition and experienced monitoring before regression of the lesions or treatment could be initiated as a worrying delay. Women expressed a fear of cancer that was not proportional to the stage of their dysplasia, but was determined by their degree of knowledge about their condition. The results suggested that although physicians are the source of information for patients, women's concerns were dependent on the quality of communication with medical practitioners and the amount of information provided.

(v) Follow-up because of an abnormal cytology result

Women with abnormal test results can be monitored by repeat cytological procedures or HPV testing after initial diagnosis (see Section 4.4.8 for HPV testing follow-up).

Kitchener et al. (2004) conducted an RCT of women attending routine screening and with recurrent BMD smear results in the United Kingdom, to determine whether a choice between colposcopy or cytological surveillance at 6 months would be beneficial to women with mildly abnormal smears in terms of psychological morbidity when compared with the national policy of surveillance at 6 months. Women were assigned to either a repeat cytology group ($n = 243$) or a choice group, in which they could choose between repeat cytology and colposcopy ($n = 233$). A survey of psychological effects was then undertaken using the GHQ and STAI questionnaires. Questionnaires were completed at baseline and repeated after initial colposcopy, if chosen, and again before and after the visit at 6 months (cytology or colposcopy) and finally at 12 months. Mean scores for GHQ and STAI state anxiety levels were no different between

the choice and no-choice groups. Both general health scores on GHQ and STAI state anxiety levels decreased over 12 months in both groups, whatever the strategy.

In the TOMBOLA trial, 3399 women aged 20–59 years with low-grade cytological abnormalities detected in the NHS Cervical Screening Programme in the United Kingdom were randomized to cytological surveillance or initial colposcopy and invited to complete a psychological questionnaire survey at recruitment and at 12, 18, 24, and 30 months. Over 30 months, women assigned to the colposcopy arm had lower scores for worries related to follow-up compared with women assigned to the cytology surveillance arm (Fielding et al., 2017). Women assigned to the colposcopy group reported lower levels of satisfaction with information and support than women assigned to the cytology surveillance group.

In a study in 1555 women aged 20–59 years referred for colposcopy after a low-grade cytology result and followed up for 30 months, 40% of women worried about having cervical cancer at one or more time point during follow-up, 26% worried about having sex, 24% worried about future fertility, and 60% worried about their general health (Sharp et al., 2015). Women diagnosed with CIN2+ had significantly higher risks of worries about cervical cancer and future fertility, and the management received was significantly associated with worries about cervical cancer and having sex. Younger women more often reported worries about future fertility.

References

Aimagambetova G, Azizan A (2018). Epidemiology of HPV infection and HPV-related cancers in Kazakhstan: a review. *Asian Pac J Cancer Prev.* 19(5):1175–80. doi:10.22034/APJCP.2018.19.5.1175 PMID:29801397

Akamatsu S, Kodama S, Himeji Y, Ikuta N, Shimagaki N (2012). A comparison of liquid-based cytology with conventional cytology in cervical cancer screening. *Acta Cytol.* 56(4):370–4. doi:10.1159/000337641 PMID:22846595

Aktanko AP, Boytsova TYU, Klimkovich NM (2018). Laboratory cytology screening results of the cervix smear-prints as a marker of intraepithelial pathological lesions. [in Russian] *Health Care of the Far East.* 2(76):51–54. Available from: https://www.elibrary.ru/item.asp?id=35586309.

Albrow R, Kitchener H, Gupta N, Desai M (2012). Cervical screening in England: the past, present, and future. *Cancer Cytopathol.* 120(2):87–96. doi:10.1002/cncy.20203 PMID:22367883

Allia E, Ronco G, Coccia A, Luparia P, Macrì L, Fiorito C, et al. (2015). Interpretation of p16INK4a/Ki-67 dual immunostaining for the triage of human papillomavirus-positive women by experts and nonexperts in cervical cytology. *Cancer Cytopathol.* 123(4):212–8. doi:10.1002/cncy.21511 PMID:25534957

Almonte M, Ferreccio C, Winkler JL, Cuzick J, Tsu V, Robles S, et al. (2007). Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. *Int J Cancer.* 121(4):796–802. doi:10.1002/ijc.22757 PMID:17437272

Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, et al. (2008). Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst.* 100(9):622–9. doi:10.1093/jnci/djn099 PMID:18445828

Andreassen T, Hansen BT, Engesæter B, Hashim D, Støer NC, Tropé A, et al. (2019). Psychological effect of cervical cancer screening when changing primary screening method from cytology to high-risk human papilloma virus testing. *Int J Cancer.* 145(1):29–39. doi:10.1002/ijc.32067 PMID:30549273

Anttila A, Pokhrel A, Kotaniemi-Talonen L, Hakama M, Malila N, Nieminen P (2011). Cervical cancer patterns with automation-assisted and conventional cytological screening: a randomized study. *Int J Cancer.* 128(5):1204–12. doi:10.1002/ijc.25677 PMID:20848590

Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al., editors (2008a). European guidelines for quality assurance in cervical cancer screening. 2nd ed. Luxembourg: Office for Official Publications of the European Communities.

Arbyn M, Bergeron C, Klinkhamer P, Martin-Hirsch P, Siebers AG, Bulten J (2008b). Liquid compared with conventional cervical cytology: a systematic review and meta-analysis. *Obstet Gynecol*. 111(1):167–77. doi:10.1097/01.AOG.0000296488.85807.b3 PMID:18165406

Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. (2020). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 8(2):e191–203. doi:10.1016/S2214-109X(19)30482-6 PMID:31812369

Aristizabal N, Cuello C, Correa P, Collazos T, Haenszel W (1984). The impact of vaginal cytology on cervical cancer risks in Cali, Colombia. *Int J Cancer*. 34(1):5–9. doi:10.1002/ijc.2910340103 PMID:6746118

Austin RM, Ramzy I (1998). Increased detection of epithelial cell abnormalities by liquid-based gynecologic cytology preparations. A review of accumulated data. *Acta Cytol*. 42(1):178–84. doi:10.1159/000331543 PMID:9479337

Bain BJ (2017). Preparation and staining methods for blood and bone marrow films. In: Bain BJ, Bates I, Laffan MA, editors. Dacie and Lewis practical haematology. 12th ed. London, UK: Elsevier; pp. 50–60.

Barchuk A, Bespalov A, Huhtala H, Chimed T, Laricheva I, Belyaev A, et al. (2018). Breast and cervical cancer incidence and mortality trends in Russia 1980–2013. *Cancer Epidemiol*. 55:73–80. doi:10.1016/j.canep.2018.05.008 PMID:29843073

Beerman H, van Dorst EBL, Kuenen-Boumeester V, Hogendoorn PCW (2009). Superior performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program. *Gynecol Oncol*. 112(3):572–6. doi:10.1016/j.ygyno.2008.12.012 PMID:19150573

Bekmukhambetov YZ, Mynbaev OA, Tinelli A, Balmagambetova SK, Koyshybaev AK, Urazayev ON, et al. (2018). Human papillomavirus related issues in western Kazakhstan: protocol for a comprehensive study. *Russian Open Medical Journal*. 7(4):e0408. doi:10.15275/rusomj.2018.0408

Benevolo M, Allia E, Gustinucci D, Rollo F, Bulletti S, Cesarini E, et al.; New Technologies for Cervical Cancer Screening 2 (NTCC2) Working Group (2017). Interobserver reproducibility of cytologic p16[INK4a]/Ki-67 dual immunostaining in human papillomavirus-positive women. *Cancer Cytopathol*. 125(3):212–20. doi:10.1002/cncy.21800 PMID:27926800

Bernstein SJ, Sanchez-Ramos L, Ndubisi B (2001). Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: a metaanalysis of prospective studies comparing cytologic diagnosis and sample adequacy. *Am J Obstet Gynecol*. 185(2):308–17. doi:10.1067/mob.2001.116736 PMID:11518884

Berrino F, Gatta G, D'Alto M, Crosignani P, Riboli E (1986). Efficacy of screening in preventing invasive cervical cancer: a case-control study in Milan, Italy. In: Hakama M, Miller AB, Day NE, editors. Screening for cancer of the uterine cervix (IARC Scientific Publications, No. 76). Lyon, France: International Agency for Research on Cancer; pp. 111–23.

Bezrukov AV (2017). Romanowsky staining, the Romanowsky effect and thoughts on the question of scientific priority. *Biotech Histochem*. 92(1):29–35. doi:10.1080/10520295.2016.1250285 PMID:28098484

Biscotti CV, Dawson AE, Dziura B, Galup L, Darragh T, Rahemtulla A, et al. (2005). Assisted primary screening using the automated ThinPrep Imaging System. *Am J Clin Pathol*. 123(2):281–7. doi:10.1309/AGB1MJ9H5N43MEGX PMID:15842055

Blanks RG, Kelly RS (2010). Comparison of cytology and histology results in English cervical screening laboratories before and after liquid-based cytology conversion: do the data provide evidence for a single category of high-grade dyskaryosis? *Cytopathology*. 21(6):368–73. doi:10.1111/j.1365-2303.2010.00808.x PMID:20955376

Bloomfield HE, Olson A, Greer N, Cantor A, MacDonald R, Rutks I, et al. (2014). Screening pelvic examinations in asymptomatic, average-risk adult women: an evidence report for a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 161(1):46–53. doi:10.7326/M13-2881 PMID:24979449

Boon ME, Drijver JS (1986). Routine cytological staining techniques: theoretical background and practice. London, UK: Palgrave. doi:10.1007/978-1-349-18250-3

Boon ME, Tabbers-Bouwmeester ML (1980). Gynaecological cytology: a textbook and atlas. London, UK: Macmillan.

Branca M, Longatto-Filho A (2015). Recommendations on quality control and quality assurance in cervical cytology. *Acta Cytol*. 59(5):361–9. doi:10.1159/000441515 PMID:26569109

Bray F, Loos AH, McCarron P, Weiderpass E, Arbyn M, Møller H, et al. (2005). Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev*. 14(3):677–86. doi:10.1158/1055-9965.EPI-04-0569 PMID:15767349

Broder S (1992). The Bethesda System for reporting cervical/vaginal cytologic diagnoses: report of the 1991 Bethesda Workshop. *JAMA*. 267(14):1892. doi:10.1001/jama.1992.03480140014005 PMID:1548812

Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. (2019a). Human papillomavirus and related diseases in Europe. Summary report. Barcelona, Spain: ICO/IARC Information Centre on HPV and Cancer. Available from: https://hpvcentre.net/statistics/reports/XEX.pdf.

Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. (2019b). Human papillomavirus and related diseases in Asia. Summary report. Barcelona, Spain: ICO/IARC Information Centre on HPV and Cancer. Available from: https://hpvcentre.net/statistics/reports/XSX.pdf.

Burghardt E (1970). The histomorphologic criteria of beginning stromal invasion in the squamous cell carcinoma of the cervix. *Minerva Ginecol*. 22(23):1142–7. PMID:4930076

Cancer Council Australia Cervical Cancer Screening Guidelines Working Party (2020). National Cervical Screening Program: guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding. Available from: https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening.

Casparie M, Tiebosch ATMG, Burger G, Blauwgeers H, van de Pol A, van Krieken JHJM, et al. (2007). Pathology databanking and biobanking in the Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol*. 29(1):19–24. PMID:17429138

Castañón A, Landy R, Cuzick J, Sasieni P (2014). Cervical screening at age 50–64 years and the risk of cervical cancer at age 65 years and older: population-based case control study. *PLoS Med*. 11(1):e1001585. doi:10.1371/journal.pmed.1001585 PMID:24453946

CDC (1997). Regulatory closure of cervical cytology laboratories: recommendations for a public health response. *MMWR Recomm Rep*. 46(RR-17):1–19. PMID:9409538

Chen C, Yang Z, Li Z, Li L (2012). Accuracy of several cervical screening strategies for early detection of cervical cancer: a meta-analysis. *Int J Gynecol Cancer*. 22(6):908–21. doi:10.1097/IGC.0b013e318256e5e4 PMID:22672987

Chernyakova AE (2016). Significance of cervical screening in diagnostics and treatment of cervical pathology. [thesis]. [in Russian] Available from: http://repo.knmu.edu.ua/bitstream/123456789/13031/1/2016_01_%D0%9C%D0%A2%D0%A2_%D0%A7%D0%B5%D1%80%D0%BD%D1%8F%D0%BA%D0%BE%D0%B2%D0%B0.pdf.

Cheung AN, Szeto EF, Leung BSY, Khoo US, Ng AWY (2003). Liquid-based cytology and conventional cervical smears: a comparison study in an Asian screening population. *Cancer*. 99(6):331–5. doi:10.1002/cncr.11786 PMID:14681939

Chicharoen SB, Tassee S, Wootipoom V, Buhachat R, Harnprasertpong J (2005). Situation analysis for management of abnormal Pap smears in the lower southern Thailand. *Asian Pac J Cancer Prev*. 6(3):286–94. PMID:16235988

Chicharoen SB, Tocharoenvanich ST (2002). Situation analysis of atypical squamous cells of undetermined significance smears in Songklanagarind Hospital. *J Obstet Gynaecol Res*. 28(5):269–73. doi:10.1046/j.1341-8076.2002.00054.x PMID:12428697

Clarke EA, Anderson TW (1979). Does screening by "Pap" smears help prevent cervical cancer? A case-control study. *Lancet*. 314(8132):1–4. https://di.org/10.1016/S0140-6736(79)90172-7doi:10.1016/S0140-6736(79)90172-7 PMID:87887

Colgan TJ, McLachlin CM, Cotterchio M, Howlett R, Seidenfeld AM, Mai VM (2004). Results of the implementation of liquid-based cytology – SurePath in the Ontario screening program. *Cancer*. 102(6):362–7. doi:10.1002/cncr.20656 PMID:15481083

College of American Pathologists (2014). Cytopathology checklist. Northfield (IL), USA: College of American Pathologists. Available from: https://webapps.cap.org/apps/docs/education/OnlineCourseContent/2014/TLTM/CYP04212014.PDF.

Colletti SM, Tranesh GA, Nassar A (2017). Significance of finding benign endometrial cells in women 40–45 versus 46 years or older on Papanicolaou tests and histologic follow-up. *Cytojournal*. 14:22. doi:10.4103/cytojournal.cytojournal_16_17 PMID:29021811

Confortini M, Bondi A, Cariaggi MP, Carozzi F, Dalla Palma P, Ghiringhello B, et al. (2007). Interlaboratory reproducibility of liquid-based equivocal cervical cytology within a randomized controlled trial framework. *Diagn Cytopathol*. 35(9):541–4. doi:10.1002/dc.20681 PMID:17703457

Confortini M, Bulgaresi P, Cariaggi MP, Carozzi FM, Cecchini S, Cipparrone I, et al. (2004). Comparing conventional and liquid-based smears from a consecutive series of 297 subjects referred to colposcopy assessment. *Cytopathology*. 15(3):168–70. doi:10.1111/j.1365-2303.2004.00142.x PMID:15165276

Cooper CP, Saraiya M (2014). Opting out of cervical cancer screening: physicians who do not perform Pap tests. *Am J Prev Med*. 47(3):315–9. doi:10.1016/j.amepre.2014.04.018 PMID:24953518

Coste J, Cochand-Priollet B, de Cremoux P, Le Galès C, Cartier I, Molinié V, et al.; French Society of Clinical Cytology Study Group (2003). Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. *BMJ*. 326(7392):733. doi:10.1136/bmj.326.7392.733 PMID:12676841

Cox JT (2009). History of the use of HPV testing in cervical screening and in the management of abnormal cervical screening results. *J Clin Virol*. 45(Suppl 1):S3–12. doi:10.1016/S1386-6532(09)70002-2 PMID:19651367

Cuschieri K, Ronco G, Lorincz A, Smith L, Ogilvie G, Mirabello L, et al. (2018). Eurogin roadmap 2017: triage strategies for the management of HPV-positive women in cervical screening programs. *Int J Cancer*. 143(4):735–45. doi:10.1002/ijc.31261 PMID:29341110

Davey E, Barratt A, Irwig L, Chan SF, Macaskill P, Mannes P, et al. (2006). Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. *Lancet*. 367(9505):122–32. doi:10.1016/S0140-6736(06)67961-0 PMID:16413876

Davey E, d'Assuncao J, Irwig L, Macaskill P, Chan SF, Richards A, et al. (2007). Accuracy of reading liquid based cytology slides using the ThinPrep Imager compared with conventional cytology: prospective study. *BMJ*. 335(7609):31. doi:10.1136/bmj.39219.645475.55 PMID:17604301

Davies P, Gentili C, Valuta D, Petrovici V, Caras O, Cuznețova T, et al. (2016). Assessment of cervical cytology services in the Republic of Moldova and recommendations for their reorganisation to comply with international evidence-based standards. Chisinau, Moldova: Ministry of Health of Moldova and United Nations Population Fund. Available from: https://moldova.unfpa.org/sites/default/files/pub-pdf/RM%20Cervical%20Cytology%20Assessment%20%20Recommendations_eng.pdf.

de Morais LSF, Magalhães JC, Braga IDS, Marega LA, Tavares SBDN, Amaral RG (2020). Performance of laboratories after 10 years of participating in external quality monitoring in cervical cytology. *Acta Cytol*. 64(3):224–31. doi:10.1159/000502433 PMID:31480038

Decker K, Demers A, Chateau D, Musto G, Nugent Z, Lotocki R, et al. (2009). Papanicolaou test utilization and frequency of screening opportunities among women diagnosed with cervical cancer. *Open Med*. 3(3):e140–7. PMID:21603052

Dickinson JA, Stankiewicz A, Popadiuk C, Pogany L, Onysko J, Miller AB (2012). Reduced cervical cancer incidence and mortality in Canada: national data from 1932 to 2006. *BMC Public Health*. 12(1):992. doi:10.1186/1471-2458-12-992 PMID:23158654

Doornewaard H, van der Schouw YT, van der Graaf Y, Bos AB, Habbema JD, van den Tweel JG (1999). The diagnostic value of computer-assisted primary cervical smear screening: a longitudinal cohort study. *Mod Pathol*. 12(11):995–1000. PMID:10574595

Duggan MA (2000). Papnet-assisted, primary screening of cervico-vaginal smears. *Eur J Gynaecol Oncol*. 21(1):35–42. PMID:10726616

Dugué PA, Lynge E, Rebolj M (2014). Mortality of non-participants in cervical screening: register-based cohort study. *Int J Cancer*. 134(11):2674–82. doi:10.1002/ijc.28586 PMID:24288241

Elit L (2014). Role of cervical screening in older women. *Maturitas*. 79(4):413–20. doi:10.1016/j.maturitas.2014.09.012 PMID:25449664

Elsheikh TM, Austin RM, Chhieng DF, Miller FS, Moriarty AT, Renshaw AA (2013). American Society of Cytopathology workload recommendations for automated Pap test screening: developed by the Productivity and Quality Assurance in the Era of Automated Screening Task Force. *Diagn Cytopathol*. 41(2):174–8. doi:10.1002/dc.22817 PMID:22351120

Farnsworth A (2016). Cervical cancer screening in Australia: past and present. *Cancer Cytopathol*. 124(4):231–4. doi:10.1002/cncy.21642 PMID:26513423

Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. (2018). Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 103:356–87. doi:10.1016/j.ejca.2018.07.005 PMID:30100160

Fiddes P, Scott A, Fletcher J, Glasier A (2003). Attitudes towards pelvic examination and chaperones: a questionnaire survey of patients and providers. *Contraception*. 67(4):313–7. doi:10.1016/S0010-7824(02)00540-1 PMID:12684154

Fielding S, Rothnie K, Gray NM, Little J, Cruickshank ME, Neal K, et al.; TOMBOLA group (2017). Psychosocial morbidity in women with abnormal cervical cytology managed by cytological surveillance or initial colposcopy: longitudinal analysis from the TOMBOLA randomised trial. *Psychooncology*. 26(4):476–83. doi:10.1002/pon.4163 PMID:27297097

Fokom-Domgue J, Combescure C, Fokom-Defo V, Tebeu PM, Vassilakos P, Kengne AP, et al. (2015). Performance of alternative strategies for primary cervical cancer screening in sub-Saharan Africa: systematic review and meta-analysis of diagnostic test accuracy studies. *BMJ*. 351:h3084. doi:10.1136/bmj.h3084 PMID:26142020

Freijomil-Vázquez C, Gastaldo D, Coronado C, Movilla-Fernández MJ (2019). Health care informational challenges for women diagnosed with cervical intraepithelial neoplasia: a qualitative study. *BMC Womens Health*. 19(1):112. doi:10.1186/s12905-019-0811-5 PMID:31477083

Fremont-Smith M, Marino J, Griffin B, Spencer L, Bolick D (2004). Comparison of the SurePath™ liquid-based Papanicolaou smear with the conventional Papanicolaou smear in a multisite direct-to-vial study. *Cancer*. 102(5):269–79. doi:10.1002/cncr.20599 PMID:15386329

French DP, Maissi E, Marteau TM (2004). Psychological costs of inadequate cervical smear test results. *Br J Cancer*. 91(11):1887–92. doi:10.1038/sj.bjc.6602224 PMID:15534608

Gage JC, Ferreccio C, Gonzales M, Arroyo R, Huivín M, Robles SC (2003). Follow-up care of women with an abnormal cytology in a low-resource setting. *Cancer Detect Prev*. 27(6):466–71. doi:10.1016/j.cdp.2003.09.004 PMID:14642555

Garau M, Musetti C, Alonso R, Barrios E (2019). Trends in cancer incidence in Uruguay: 2002–2015. *Colomb Med (Cali)*. 50(4):224–38. doi:10.25100/cm.v50i4.4212 PMID:32476689

Giorgi-Rossi P, Franceschi S, Ronco G (2012). HPV prevalence and accuracy of HPV testing to detect high-grade cervical intraepithelial neoplasia. *Int J Cancer*. 130(6):1387–94. doi:10.1002/ijc.26147 PMID:21520039

Grada Z, Paquette C, Eklund CM, Zhang C, Sung CJ, Steinhoff M, et al. (2017). Evaluating the age cutoff criterion for reporting benign-appearing endometrial cells in routine Pap tests: an 8-year retrospective review. *Acta Cytol*. 61(3):194–8. doi:10.1159/000473694 PMID:28486237

Gray NM, Sharp L, Cotton SC, Masson LF, Little J, Walker LG, et al.; TOMBOLA group (2006). Psychological effects of a low-grade abnormal cervical smear test result: anxiety and associated factors. *Br J Cancer*. 94(9):1253–62. doi:10.1038/sj.bjc.6603086 PMID:16622462

Grebenkina EV, Guryanova AV, Ushakova MS, Belova SV, Smetanina SV, Zhelezin OV (2018). The work of the Reference Cytological Center, including the early diagnosis of cervical cancer in the Nizhny Novgorod Region. [in Russian] *Oncol Bull Volga Region*. 9(3).

Grjibovski AM, Dubovichenko D, Saduakassova S, Zhatkanbayeva G, Omarova G, Shalgumbayeva G, et al. (2018). Incidence, mortality and determinants of survival from cervical cancer in northwest Russia: a registry-based cohort study. *Int Health*. 10(2):92–9. doi:10.1093/inthealth/ihx068 PMID:29432549

Gupta R, Gupta S, Mehrotra R, Sodhani P (2017). Cervical cancer screening in resource-constrained countries: current status and future directions. *Asian Pac J Cancer Prev*. 18(6):1461–7. doi:10.22034/apjcp.2017.18.6.1461 PMID:28669152

Gustinucci D, Giorgi Rossi P, Cesarini E, Broccolini M, Bulletti S, Carlani A, et al. (2016). Use of cytology, E6/E7 mRNA, and p16^{INK4a}-Ki-67 to define the management of human papillomavirus (HPV)-positive women in cervical cancer screening. *Am J Clin Pathol*. 145(1):35–45. doi:10.1093/ajcp/aqv019 PMID:26712869

Halford JA, Batty T, Boost T, Duhig J, Hall J, Lee C, et al. (2010). Comparison of the sensitivity of conventional cytology and the ThinPrep Imaging System for 1,083 biopsy confirmed high-grade squamous lesions. *Diagn Cytopathol*. 38(5):318–26. doi:10.1002/dc.21199 PMID:19813268

Herbert A, Anic V, Cochand-Priollet B, Dina R, Ehya H, Eide ML, et al. (2014). Training and practice of cytotechnologists: a discussion forum focused on Europe. *Cytopathology*. 25(5):307–15. doi:10.1111/cyt.12201 PMID:25209399

Herbert A, Stein K, Bryant TN, Breen C, Old P (1996). Relation between the incidence of invasive cervical cancer and the screening interval: is a five year interval too long? *J Med Screen*. 3(3):140–5. doi:10.1177/096914139600300307 PMID:8946309

Hernández-Avila M, Lazcano-Ponce EC, de Ruíz PA, Romieu I (1998). Evaluation of the cervical cancer screening programme in Mexico: a population-based case-control study. *Int J Epidemiol*. 27(3):370–6. doi:10.1093/ije/27.3.370 PMID:9698122

Herrero R, Brinton LA, Reeves WC, Brenes MM, de Britton RC, Gaitan E, et al. (1992). Screening for cervical cancer in Latin America: a case-control study. *Int J Epidemiol*. 21(6):1050–6. doi:10.1093/ije/21.6.1050 PMID:1336485

Herrero R, Brinton LA, Reeves WC, Brenes MM, Tenorio F, de Britton RC, et al. (1990). Risk factors for invasive carcinoma of the uterine cervix in Latin America. *Bull Pan Am Health Organ*. 24(3):263–83. PMID:2171706

Hilgarth M (2001). Munich II nomenclature for gynaecological cytodiagnosis of the cervix. *Frauenarzt*. 39:392–3.

Hinson S, Molberg K, Mir M, Flores M, Zheng W, Lucas E (2019). Age cutoff for reporting of benign-appearing endometrial cells in Papanicolaou specimens; should it be raised? A 10-year retrospective study from a large county hospital. *J Am Soc Cytopathol*. 8(2):78–83. doi:10.1016/j.jasc.2018.09.002 PMID:31287423

Hoffman M, Cooper D, Carrara H, Rosenberg L, Kelly J, Stander I, et al. (2003). Limited Pap screening associated with reduced risk of cervical cancer in South Africa. *Int J Epidemiol*. 32(4):573–7. doi:10.1093/ije/dyg081 PMID:12913031

Horobin RW (2011). How Romanowsky stains work and why they remain valuable – including a proposed universal Romanowsky staining mechanism and a rational troubleshooting scheme. *Biotech Histochem*. 86(1):36–51. doi:10.3109/10520295.2010.515491 PMID:21235292

Hosono S, Terasawa T, Katayama T, Sasaki S, Hoshi K, Hamashima C (2018). Frequency of unsatisfactory cervical cytology smears in cancer screening of Japanese women: a systematic review and meta-analysis. *Cancer Sci*. 109(4):934–43. doi:10.1111/cas.13549 PMID:29478281

Hoyo C, Yarnall KSH, Skinner CS, Moorman PG, Sellers D, Reid L (2005). Pain predicts non-adherence to Pap smear screening among middle-aged African American women. *Prev Med*. 41(2):439–45. doi:10.1016/j.ypmed.2004.11.021 PMID:15917039

Hu Y, Hong Z, Gu L, Xie L, Yang B, Dai H, et al. (2020). Evaluation of p16/Ki-67 dual-stained cytology in triaging HPV-positive women during cervical cancer screening. *Cancer Epidemiol Biomarkers Prev*. 29(6):1246–52. doi:10.1158/1055-9965.EPI-19-1180 PMID:32156721

IARC (1986). Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. IARC Working Group on evaluation of cervical cancer screening programmes. *Br Med J (Clin Res*

Ed). 293(6548):659–64. doi:10.1136/bmj.293.6548.659 PMID:3092971

IARC (2005). Cervix cancer screening. *IARC Handb Cancer Prev*. 10:1–302. Available from: https://publications.iarc.fr/380.

IARC (2012). Current status and future directions of breast and cervical cancer prevention and early detection in Belarus (IARC Working Group Reports, Volume 6). Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/389.

Ideström M, Milsom I, Andersson-Ellström A (2003). Women's experience of coping with a positive Pap smear: a register-based study of women with two consecutive Pap smears reported as CIN 1. *Acta Obstet Gynecol Scand*. 82(8):756–61.doi:10.1034/j.1600-0412.2003.00165.x PMID:12848648

Ideström M, Milsom I, Andersson-Ellström A (2007). The cervical cancer screening program from a midwife's perspective. *Acta Obstet Gynecol Scand*. 86(6):742–8. doi:10.1080/00016340701371272 PMID:17520410

Ikenberg H, Bergeron C, Schmidt D, Griesser H, Alameda F, Angeloni C, et al.; PALMS Study Group (2013). Screening for cervical cancer precursors with p16/Ki-67 dual-stained cytology: results of the PALMS study. *J Natl Cancer Inst*. 105(20):1550–7. doi:10.1093/jnci/djt235 PMID:24096620

International Collaboration of Epidemiological Studies of Cervical Cancer (2007). Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer*. 120(4):885–91. doi:10.1002/ijc.22357 PMID:17131323

Iskhakova GS, Imelbaeva EA, Amineva RKh (2012). Experience of a centralized cytological laboratory in the central regional hospital of the small town Meleuz. [in Russian] *Clinical Cytology News in Russia*. 16(1–2).

Ito K, Kimura R, Konishi H, Ozawa N, Yaegashi N, Ohashi Y, et al. (2020). A comparison of liquid-based and conventional cytology using data for cervical cancer screening from the Japan Cancer Society. *Jpn J Clin Oncol*. 50(2):138–44. doi:10.1093/jjco/hyz161 PMID:31735963

Jarynowski A (2019). Cost-effectiveness analysis for HPV mitigation strategies in the Republic of Moldova based on infectious disease modelling. *Econ Sociol*. 2:50–64. doi:10.36004/nier.es.2019.2-05

Jiang MY, Wu Z, Li T, Yu L, Zhang SK, Zhang X, et al. (2020). Performance of HPV genotyping combined with p16/Ki-67 in detection of cervical precancer and cancer among HPV-positive Chinese women. *Cancer Prev Res (Phila)*. 13(2):163–72. doi:10.1158/1940-6207.CAPR-19-0144 PMID:31871224

Jiménez-Pérez M, Thomas DB (1999). Has the use of Pap smears reduced the risk of invasive cervical cancer in Guadalajara, Mexico? *Int J Cancer*. 82(6):804–9. doi:10.1002/(SICI)1097-0215(19990909)82:6<804::AID-IJC6>3.0.CO;2-N PMID:10446445

Jun JK, Choi KS, Jung KW, Lee HY, Gapstur SM, Park EC, et al. (2009). Effectiveness of an organized cervical cancer screening program in Korea: results from a cohort study. *Int J Cancer*. 124(1):188–93. doi:10.1002/ijc.23841 PMID:18785204

Kahn JA, Goodman E, Huang B, Slap GB, Emans SJ (2003). Predictors of Papanicolaou smear return in a hospital-based adolescent and young adult clinic. *Obstet Gynecol*. 101(3):490–9. doi:10.1016/S0029-7844(02)02592-9 PMID:12636952

Kamineni A, Weinmann S, Shy KK, Glass AG, Weiss NS (2013). Efficacy of screening in preventing cervical cancer among older women. *Cancer Causes Control*. 24(9):1653–60. doi:10.1007/s10552-013-0239-4 PMID:23744043

Kasinpila C, Promthet S, Vatanasapt P, Sasieni P, Parkin DM (2011). Evaluation of the nationwide cervical screening programme in Thailand: a case-control study. *J Med Screen*. 18(3):147–53. doi:10.1258/jms.2011.011075 PMID:22045824

Kirillina MP, Ivanova AK, Lushnikova EL (2018). Cytological analysis of cervix inflammatory diseases in different age groups on the example of the Sakha (Yakutia) Republic. *Yakut Medical Journal*. 4(64):12–5. doi:10.25789/YMJ.2018.64.03

Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al. (2009). HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol*. 10(7):672–82. doi:10.1016/S1470-2045(09)70156-1 PMID:19540162

Kitchener HC, Blanks R, Dunn G, Gunn L, Desai M, Albrow R, et al. (2011). Automation-assisted versus manual reading of cervical cytology (MAVARIC): a randomised controlled trial. *Lancet Oncol*. 12(1):56–64. doi:10.1016/S1470-2045(10)70264-3 PMID:21146458

Kitchener HC, Burns S, Nelson L, Myers AJ, Fletcher I, Desai M, et al. (2004). A randomised controlled trial of cytological surveillance versus patient choice between surveillance and colposcopy in managing mildly abnormal cervical smears. *BJOG*. 111(1):63–70. doi:10.1046/j.1471-0528.2003.00007.x PMID:14687054

Kituncharoen S, Tantbirojn P, Niruthisard S (2015). Comparison of unsatisfactory rates and detection of abnormal cervical cytology between conventional Papanicolaou smear and liquid-based cytology (Sure Path®). *Asian Pac J Cancer Prev*. 16(18):8491–4. doi:10.7314/apjcp.2015.16.18.8491 PMID:26745107

Klaes R, Friedrich T, Spitkovsky D, Ridder R, Rudy W, Petry U, et al. (2001). Overexpression of p16[INK4A] as a specific marker for dysplastic and neoplastic epithelial

cells of the cervix uteri. *Int J Cancer.* 92(2):276–84. doi:10.1002/ijc.1174 PMID:11291057

Klug SJ, Neis KJ, Harlfinger W, Malter A, König J, Spieth S, et al. (2013). A randomized trial comparing conventional cytology to liquid-based cytology and computer assistance. *Int J Cancer.* 132(12):2849–57. doi:10.1002/ijc.27955 PMID:23175270

Kok MR, Boon ME (1996). Consequences of neural network technology for cervical screening: increase in diagnostic consistency and positive scores. *Cancer.* 78(1):112–7. doi:10.1002/(SICI)1097-0142(19960701)78:1<112::AID-CNCR16>3.0.CO;2-2 PMID:8646706

Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PPL, Mustafa RA, et al. (2017). Cytology versus HPV testing for cervical cancer screening in the general population. *Cochrane Database Syst Rev.* 8:CD008587. doi:10.1002/14651858.CD008587.pub2 PMID:28796882

Korfage IJ, van Ballegooijen M, Huveneers H, Essink-Bot ML (2010). Anxiety and borderline Pap smear results. *Eur J Cancer.* 46(1):134–41. doi:10.1016/j.ejca.2009.07.003 PMID:19683428

Korfage IJ, van Ballegooijen M, Wauben B, Looman CWN, Habbema JDF, Essink-Bot ML (2012). Having a Pap smear, quality of life before and after cervical screening: a questionnaire study. *BJOG.* 119(8):936–44. doi:10.1111/j.1471-0528.2012.03344.x PMID:22568482

Kozyreva SM, et al. (2012). On the clinical and morphological diagnosis of cervical neoplasms by ploidometry. [in Russian] *Bull New Med Technol.* 14(1):137.

Krafts KP, Pambuccian SE (2011). Romanowsky staining in cytopathology: history, advantages and limitations. *Biotech Histochem.* 86(2):82–93. doi:10.3109/10520295.2010.515492 PMID:21395493

Kurtycz DFI, Staats PN, Chute DJ, Russell D, Pavelec D, Monaco SE, et al. (2017). Bethesda Interobserver Reproducibility Study-2 (BIRST-2): Bethesda System 2014. *J Am Soc Cytopathol.* 6(4):131–44. doi:10.1016/j.jasc.2017.03.003 PMID:31043266

La Vecchia C, Bosetti C, Lucchini F, Bertuccio P, Negri E, Boyle P, et al. (2010). Cancer mortality in Europe, 2000–2004, and an overview of trends since 1975. *Ann Oncol.* 21(6):1323–60. doi:10.1093/annonc/mdp530 PMID:19948741

La Vecchia C, Franceschi S, Decarli A, Fasoli M, Gentile A, Tognoni G (1984). "Pap" smear and the risk of cervical neoplasia: quantitative estimates from a case-control study. *Lancet.* 342(8406):779–82. doi:10.1016/S0140-6736(84)90705-0 PMID:6148523

Larsen M, Oldeide CC, Malterud K (1997). Not so bad after all… Women's experiences of pelvic examinations. *Fam Pract.* 14(2):148–52. doi:10.1093/fampra/14.2.148 PMID:9137954

Lee Mortensen G, Adeler AL (2010). Qualitative study of women's anxiety and information needs after a diagnosis of cervical dysplasia. *J Public Health.* 18(5):473–82. doi:10.1007/s10389-010-0330-1 PMID:21151479

Lei J, Andrae B, Ploner A, Lagheden C, Eklund C, Nordqvist Kleppe S, et al. (2019). Cervical screening and risk of adenosquamous and rare histological types of invasive cervical carcinoma: population based nested case-control study. *BMJ.* 365:l1207. doi:10.1136/bmj.l1207 PMID:30944091

Li Q, Weina PJ, Miller RS (2012). Malaria analysis. In: Kottke-Marchant K, Davis BH, editors. Laboratory hematology practice. 1st ed. Oxford, UK: Wiley-Blackwell; pp. 626–37. doi:10.1002/9781444398595.ch48

Lönnberg S, Anttila A, Luostarinen T, Nieminen P (2012). Age-specific effectiveness of the Finnish cervical cancer screening programme. *Cancer Epidemiol Biomarkers Prev.* 21(8):1354–61. doi:10.1158/1055-9965.EPI-12-0162 PMID:22665576

Lönnberg S, Nieminen P, Luostarinen T, Anttila A (2013). Mortality audit of the Finnish cervical cancer screening program. *Int J Cancer.* 132(9):2134–40. doi:10.1002/ijc.27844 PMID:22987437

Maccallini V, Angeloni C, Caraceni D, Fortunato C, Venditti MA, Di Gabriele G, et al. (2008). Comparison of the conventional cervical smear and liquid-based cytology: results of a controlled, prospective study in the Abruzzo region of Italy. *Acta Cytol.* 52(5):568–74. doi:10.1159/000325599 PMID:18833819

Maissi E, Marteau TM, Hankins M, Moss S, Legood R, Gray A (2004). Psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: cross sectional questionnaire study. *BMJ.* 328(7451):1293. doi:10.1136/bmj.328.7451.1293 PMID:15166066

Makino H, Sato S, Yajima A, Komatsu S, Fukao A (1995). Evaluation of the effectiveness of cervical cancer screening: a case-control study in Miyagi, Japan. *Tohoku J Exp Med.* 175(3):171–8. doi:10.1620/tjem.175.171 PMID:7792786

Maksem JA, Finnemore M, Belsheim BL, Roose EB, Makkapati SR, Eatwell L, et al. (2001). Manual method for liquid-based cytology: a demonstration using 1,000 gynecological cytologies collected directly to vial and prepared by a smear-slide technique. *Diagn Cytopathol.* 25(5):334–8. doi:10.1002/dc.2166 PMID:11747227

Marshall PN (1978). Romanowsky-type stains in haematology. *Histochem J.* 10(1):1–29. doi:10.1007/BF01003411 PMID:74370

Martin-Hirsch PPL, Jarvis GG, Kitchener HC, Lilford R (2000). Collection devices for obtaining cervical cytology samples. *Cochrane Database Syst Rev.* (2):CD001036. doi:10.1002/14651858.CD001036 PMID:10796736

Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al.; 2012 ASCCP Consensus Guidelines Conference (2013). 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol*. 121(4):829–46. doi:10.1097/AOG.0b013e3182883a34 PMID:23635684

McCredie MRE, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. (2008). Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*. 9(5):425–34. doi:10.1016/S1470-2045(08)70103-7 PMID:18407790

McDonald P, Herity B, Johnson Z, O'Kelly F (2001). Views of Irish general practitioners on screening for cervical cancer. *Ir J Med Sci*. 170(3):186–8. doi:10.1007/BF03173887 PMID:12120972

Mendes D, Mesher D, Pista A, Baguelin M, Jit M (2018). Understanding differences in cervical cancer incidence in Western Europe: comparing Portugal and England. *Eur J Public Health*. 28(2):343–7. doi:10.1093/eurpub/ckx176 PMID:29059348

Miller MG, Sung HY, Sawaya GF, Kearney KA, Kinney W, Hiatt RA (2003). Screening interval and risk of invasive squamous cell cervical cancer. *Obstet Gynecol*. 101(1):29–37. doi:10.1016/s0029-7844(02)02454-7 PMID:12517642

Ministry of Health of the Russian Federation (2019). Order of the Ministry of Health of the Russian Federation of March 13, 2019, No 124n. On approval of the procedure for conducting preventive medical examination and clinical examination of certain groups of the adult population. Moscow, Russian Federation: Ministry of Health of the Russian Federation.

Mitchell HS (2001). Longitudinal analysis of histologic high-grade disease after negative cervical cytology according to endocervical status. *Cancer*. 93(4):237–40. doi:10.1002/cncr.9035 PMID:11507695

Mody DR, Davey DD, Branca M, Raab SS, Schenck UG, Stanley MW, et al. (2000). Quality assurance and risk reduction guidelines. *Acta Cytol*. 44(4):496–507. doi:10.1159/000328521 PMID:10934940

Moettus A, Sklar D, Tandberg D (1999). The effect of physician gender on women's perceived pain and embarrassment during pelvic examination. *Am J Emerg Med*. 17(7):635–7. doi:10.1016/S0735-6757(99)90148-1 PMID:10597078

Morrison AS (1992). Screening in chronic disease. Monographs in Epidemiology and Biostatistics. Oxford, UK: Oxford University Press.

Murillo R, Cendales R, Wiesner C, Piñeros M, Tovar S (2009). Effectiveness of cytology-based cervical cancer screening in the Colombian health system. [in Spanish] *Biomedica*. 29(3):354–61. doi:10.7705/biomedica.v29i3.7 PMID:20436987

Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. (2016). Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. *Int J Gynaecol Obstet*. 132(3):259–65. doi:10.1016/j.ijgo.2015.07.024 PMID:26851054

Nanda K, McCrory DC, Myers ER, Bastian LA, Hasselblad V, Hickey JD, et al. (2000). Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med*. 132(10):810–9. doi:10.7326/0003-4819-132-10-200005160-00009 PMID:10819705

Nandini NM, Nandish SM, Pallavi P, Akshatha SK, Chandrashekhar AP, Anjali S, et al. (2012). Manual liquid based cytology in primary screening for cervical cancer – a cost effective preposition for scarce resource settings. *Asian Pac J Cancer Prev*. 13(8):3645–51. doi:10.7314/APJCP.2012.13.8.3645 PMID:23098448

Nascimento MI, Silva GA, Monteiro GT (2012). [Previous history of Pap smears and cervical cancer: a case-control study in the Baixada Fluminense, Rio de Janeiro State, Brazil]. *Cad Saude Publica*. 28(10):1841–53. [Portuguese]doi:10.1590/S0102-311X2012001000004 PMID:23090165

National Institute for Health and Clinical Excellence (2003). Guidance on the use of liquid-based cytology for cervical screening: technology appraisal guidance. London, UK: National Institute for Health and Clinical Excellence. Available from: https://www.nice.org.uk/guidance/TA69.

National Pathology Accreditation Advisory Council (2019). Requirements for laboratories reporting tests for the National Cervical Screening Program (second edition 2019). Canberra, Australia: Australia Department of Health. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/npaac-cervical-screening.

Nayar R, Wilbur DC (2015). The Pap test and Bethesda 2014. *Cancer Cytopathol*. 123(5):271–81. doi:10.1002/cncy.21521 PMID:25931431

Nieminen P, Hakama M, Viikki M, Tarkkanen J, Anttila A (2003). Prospective and randomised public-health trial on neural network-assisted screening for cervical cancer in Finland: results of the first year. *Int J Cancer*. 103(3):422–6. doi:10.1002/ijc.10839 PMID:12471627

Nieminen P, Kallio M, Anttila A, Hakama M (1999). Organised vs. spontaneous Pap-smear screening for cervical cancer: a case-control study. *Int J Cancer*. 83(1):55–8. doi:10.1002/(SICI)1097-0215(19990924)83:1<55::AID-IJC11>3.0.CO;2-U PMID:10449608

Nieminen P, Kotaniemi-Talonen L, Hakama M, Tarkkanen J, Martikainen J, Toivonen T, et al. (2007). Randomized evaluation trial on automation-assisted screening for cervical cancer: results after 777,000 invitations. *J Med Screen*. 14(1):23–8. doi:10.1258/096914107780154468 PMID:17362568

Norrell LL, Kuppermann M, Moghadassi MN, Sawaya GF (2017). Women's beliefs about the purpose and value of routine pelvic examinations. *Am J Obstet Gynecol.* 217(1):86.e1–6. doi:10.1016/j.ajog.2016.12.031 PMID:28040449

Obwegeser JH, Brack S (2001). Does liquid-based technology really improve detection of cervical neoplasia? A prospective, randomized trial comparing the ThinPrep Pap Test with the conventional Pap Test, including follow-up of HSIL cases. *Acta Cytol.* 45(5):709–14. doi:10.1159/000328292 PMID:11575648

Odongua N, Chae YM, Kim MR, Yun JE, Jee SH (2007). Associations between smoking, screening, and death caused by cervical cancer in Korean women. *Yonsei Med J.* 48(2):192–200. doi:10.3349/ymj.2007.48.2.192 PMID:17461516

Ogilvie GS, Krajden M, van Niekerk D, Smith LW, Cook D, Ceballos K, et al. (2017). HPV For Cervical Cancer Screening (HPV FOCAL): complete round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer. *Int J Cancer.* 140(2):440–8. doi:10.1002/ijc.30454 PMID:27685757

Olson B, Gribble B, Dias J, Curryer C, Vo K, Kowal P, et al. (2016). Cervical cancer screening programs and guidelines in low- and middle-income countries. *Int J Gynaecol Obstet.* 134(3):239–46. doi:10.1016/j.ijgo.2016.03.011 PMID:27350227

Padma S, Ramana PV Kante R, Shravan Kumar O (2018). A comparative study of staining characteristics of Leishman-Geimsa cocktail and Papanicolaou stain in cervical cytology. *Asian Pac. J. Health Sci.* 5(3):233–6. doi:10.21276/apjhs.2018.5.3.32

Pankaj S, Nazneen S, Kumari S, Kumari A, Kumari A, Kumari J, et al. (2018). Comparison of conventional Pap smear and liquid-based cytology: a study of cervical cancer screening at a tertiary care center in Bihar. *Indian J Cancer.* 55(1):80–3. doi:10.4103/ijc.IJC_352_17 PMID:30147099

Pankakoski M, Anttila A, Sarkeala T, Heinävaara S (2019). Effectiveness of cervical cancer screening at age 65 – a register-based cohort study. *PLoS One.* 14(3):e0214486. doi:10.1371/journal.pone.0214486 PMID:30913262

Park Y, Vongdala C, Kim J, Ki M (2015). Changing trends in the incidence (1999–2011) and mortality (1983–2013) of cervical cancer in the Republic of Korea. *Epidemiol Health.* 37:e2015024. doi:10.4178/epih/e2015024 PMID:26063351

Payne N, Chilcott J, McGoogan E (2000). Liquid-based cytology in cervical screening: a rapid and systematic review. *Health Technol Assess.* 4(18):1–73. doi:10.3310/hta4180 PMID:10932023

Pedersen K, Fogelberg S, Thamsborg LH, Clements M, Nygård M, Kristiansen IS, et al. (2018). An overview of cervical cancer epidemiology and prevention in Scandinavia. *Acta Obstet Gynecol Scand.* 97(7):795–807. doi:10.1111/aogs.13313 PMID:29388202

Peeters E, Wentzensen N, Bergeron C, Arbyn M (2019). Meta-analysis of the accuracy of p16 or p16/Ki-67 immunocytochemistry versus HPV testing for the detection of CIN2+/CIN3+ in triage of women with minor abnormal cytology. *Cancer Cytopathol.* 127(3):169–80. doi:10.1002/cncy.22103 PMID:30811902

Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R (2013). Screening for cervical cancer: a systematic review and meta-analysis. *Syst Rev.* 2(1):35. doi:10.1186/2046-4053-2-35 PMID:23706117

Petry KU, Menton S, Menton M, van Loenen-Frosch F, de Carvalho Gomes H, Holz B, et al. (2003). Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *Br J Cancer.* 88(10):1570–7. doi:10.1038/sj.bjc.6600918 PMID:12771924

Petry KU, Schmidt D, Scherbring S, Luyten A, Reinecke-Lüthge A, Bergeron C, et al. (2011). Triaging Pap cytology negative, HPV positive cervical cancer screening results with p16/Ki-67 dual-stained cytology. *Gynecol Oncol.* 121(3):505–9. doi:10.1016/j.ygyno.2011.02.033 PMID:21420158

Phaliwong P, Pariyawateekul P, Khuakoonratt N, Sirichai W, Bhamarapravatana K, Suwannarurk K (2018). Cervical cancer detection between conventional and liquid based cervical cytology: a 6-year experience in northern Bangkok Thailand. *Asian Pac J Cancer Prev.* 19(5):1331–6. doi:10.22034/apjcp.2018.19.5.1331 PMID:29802695

Pilleron S, Cabasag CJ, Ferlay J, Bray F, Luciani S, Almonte M, et al. (2020). Cervical cancer burden in Latin America and the Caribbean: where are we? *Int J Cancer.* 147(6):1638–48. doi:10.1002/ijc.32956 PMID:32150288

Pirotta M, Ung L, Stein A, Conway EL, Mast TC, Fairley CK, et al. (2009). The psychosocial burden of human papillomavirus related disease and screening interventions. *Sex Transm Infect.* 85(7):508–13. doi:10.1136/sti.2009.037028 PMID:19703844

Public Health England (2016). NHS Cervical Screening Programme: colposcopy and programme management. 3rd ed. London, UK: Public Health England. Available from: https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management.

Public Health England (2019a). Cervical screening: guidance for laboratories providing HPV testing and cytology services in the NHS Cervical Screening Programme. Available from: https://www.gov.uk/government/publications/cervical-screening-laboratory-hpv-testing-and-cytology-services.

Public Health England (2019b). NHS Cervical Screening Programme (CSP): liquid-based cytology system conversion training. Available from: https://www.gov.uk/government/publications/

cervical-screening-training-to-use-a-new-cytology-system.

Public Health England (2020). Education pathway. Available from: https://www.gov.uk/government/publications/cervical-screening-cervical-sample-taker-training.

Rebolj M, Rask J, van Ballegooijen M, Kirschner B, Rozemeijer K, Bonde J, et al. (2015). Cervical histology after routine ThinPrep or SurePath liquid-based cytology and computer-assisted reading in Denmark. *Br J Cancer*. 113(9):1259–74. doi:10.1038/bjc.2015.339 PMID:26448176

Rebolj M, van Ballegooijen M, Lynge E, Looman C, Essink-Bot ML, Boer R, et al. (2009). Incidence of cervical cancer after several negative smear results by age 50: prospective observational study. *BMJ*. 338:b1354. doi:10.1136/bmj.b1354 PMID:19395420

Reis NVS, Andrade BB, Guerra MR, Teixeira MTB, Malta DC, Passos VMA (2020). The Global Burden of Disease Study estimates of Brazil's cervical cancer burden. *Ann Glob Health*. 86(1):56. doi:10.5334/aogh.2756 PMID:32566484

Renshaw AA, Elsheikh TM (2013). Assessment of manual workload limits in gynecologic cytology: reconciling data from 3 major prospective trials of automated screening devices. *Am J Clin Pathol*. 139(4):428–33. doi:10.1309/AJCP23YDFKKQNUAO PMID:23525612

Roelens J, Reuschenbach M, von Knebel-Doeberitz M, Wentzensen N, Bergeron C, Arbyn M (2012). p16INK4a immunocytochemistry versus HPV testing for triage of women with minor cytological abnormalities: a systematic review and meta-analysis. *Cancer Cytopathol*. 120(5):294–307. doi:10.1002/cncy.21205 PMID:22700382

Rogovskaya SI, Shabalova IP, Mikheeva IV, Minkina GN, Podzolkova NM, Shipulina OY, et al. (2013). Human papillomavirus prevalence and type-distribution, cervical cancer screening practices and current status of vaccination implementation in Russian Federation, the western countries of the former Soviet Union, Caucasus region and Central Asia. *Vaccine*. 31(Suppl 7): H46–58. doi:10.1016/j.vaccine.2013.06.043 PMID:24332297

Ronco G, Cuzick J, Pierotti P, Cariaggi MP, Dalla Palma P, Naldoni C, et al. (2007). Accuracy of liquid based versus conventional cytology: overall results of New Technologies for Cervical Cancer Screening randomised controlled trial. *BMJ*. 335(7609):28. doi:10.1136/bmj.39196.740995.BE PMID:17517761

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al.; New Technologies for Cervical Cancer Screening Working Group (2008). Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical

cancer screening test. *J Natl Cancer Inst*. 100(7):492–501. doi:10.1093/jnci/djn065 PMID:18364502

Ronco G, Giorgi-Rossi P, Carozzi F, Dalla Palma P, Del Mistro A, De Marco L, et al.; New Technologies for Cervical Cancer Screening Working Group (2006). Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. *Lancet Oncol*. 7(7):547–55. doi:10.1016/S1470-2045(06)70731-8 PMID:16814206

Ronco G, Montanari G, Confortini M, Parisio F, Berardengo E, Delpiano AM, et al. (2003). Effect of circulation and discussion of cervical smears on agreement between laboratories. *Cytopathology*. 14(3):115–20. doi:10.1046/j.1365-2303.2003.00035.x PMID:12828719

Ronco G, van Ballegooijen M, Becker N, Chil A, Fender M, Giubilato P, et al. (2009). Process performance of cervical screening programmes in Europe. *Eur J Cancer*. 45(15):2659–70. doi:10.1016/j.ejca.2009.07.022 PMID:19713100

Rosenblatt KA, Osterbur EF, Douglas JA (2016). Case-control study of cervical cancer and gynecologic screening: a SEER-Medicare analysis. *Gynecol Oncol*. 142(3):395–400. doi:10.1016/j.ygyno.2016.06.016 PMID:27388696

Rozemeijer K, Naber SK, Penning C, Overbeek LIH, Looman CWN, de Kok IMCM, et al. (2017). Cervical cancer incidence after normal cytological sample in routine screening using SurePath, ThinPrep, and conventional cytology: population based study. *BMJ*. 356:j504. doi:10.1136/bmj.j504 PMID:28196844

Rozemeijer K, Penning C, Siebers AG, Naber SK, Matthijsse SM, van Ballegooijen M, et al. (2016). Comparing SurePath, ThinPrep, and conventional cytology as primary test method: SurePath is associated with increased CIN II+ detection rates. *Cancer Causes Control*. 27(1):15–25. doi:10.1007/s10552-015-0678-1 PMID:26458884

Rustagi AS, Kamineni A, Weinmann S, Reed SD, Newcomb P, Weiss NS (2014). Cervical screening and cervical cancer death among older women: a population-based, case-control study. *Am J Epidemiol*. 179(9):1107–14. doi:10.1093/aje/kwu035 PMID:24685531

Sankaranarayanan R, Nene BM, Dinshaw KA, Mahe C, Jayant K, Shastri SS, et al.; Osmanabad District Cervical Screening Study Group (2005). A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer*. 116(4):617–23. doi:10.1002/ijc.21050 PMID:15818610

Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. (2009). HPV screening for cervical cancer in rural India. *N Engl J Med*. 360(14):1385–94. doi:10.1056/NEJMoa0808516 PMID:19339719

Sasieni P, Adams J, Cuzick J (2003). Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer*. 89(1):88–93. doi:10.1038/sj.bjc.6600974 PMID:12838306

Sasieni P, Castanon A, Cuzick J (2009). Screening and adenocarcinoma of the cervix. *Int J Cancer*. 125(3):525–9. doi:10.1002/ijc.24410 PMID:19449379

Sasieni PD, Cuzick J, Lynch-Farmery E; The National Co-ordinating Network for Cervical Screening Working Group (1996). Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. *Br J Cancer*. 73(8):1001–5. doi:10.1038/bjc.1996.196 PMID:8611418

Schmidt D, Bergeron C, Denton KJ, Ridder R; European CINtec Cytology Study Group (2011). p16/Ki-67 dual-stain cytology in the triage of ASCUS and LSIL Papanicolaou cytology: results from the European Equivocal or Mildly Abnormal Papanicolaou Cytology study. *Cancer Cytopathol*. 119(3):158–66. doi:10.1002/cncy.20140 PMID:21442767

Schneider A, Hoyer H, Lotz B, Leistritza S, Kühne-Heid R, Nindl I, et al. (2000). Screening for high-grade cervical intra-epithelial neoplasia and cancer by testing for high-risk HPV, routine cytology or colposcopy. *Int J Cancer*. 89(6):529–34. doi:10.1002/1097-0215(20001120)89:6<529::AID-IJC11>3.0.CO;2-G PMID:11102899

Seehusen DA, Johnson DR, Earwood JS, Sethuraman SN, Cornali J, Gillespie K, et al. (2006). Improving women's experience during speculum examinations at routine gynaecological visits: randomised clinical trial. *BMJ*. 333(7560):171. doi:10.1136/bmj.38888.588519.55 PMID:16803941

Sepúlveda C, Prado R (2005). Effective cervical cytology screening programmes in middle-income countries: the Chilean experience. *Cancer Detect Prev*. 29(5):405–11. doi:10.1016/j.cdp.2005.07.001 PMID:16188399

Sharp L, Cotton SC, Cruickshank ME, Gray NM, Neal K, Rothnie K, et al.; TOMBOLA Group (2015). Long-term worries after colposcopy: which women are at increased risk? *Womens Health Issues*. 25(5):517–27. doi:10.1016/j.whi.2015.04.002 PMID:26051021

Sherman ME, Dasgupta A, Schiffman M, Nayar R, Solomon D (2007). The Bethesda Interobserver Reproducibility Study (BIRST): a web-based assessment of the Bethesda 2001 System for classifying cervical cytology. *Cancer*. 111(1):15–25. doi:10.1002/cncr.22423 PMID:17186503

Siebers AG, Klinkhamer PJJM, Arbyn M, Raifu AO, Massuger LFAG, Bulten J (2008). Cytologic detection of cervical abnormalities using liquid-based compared with conventional cytology: a randomized controlled trial. *Obstet Gynecol*. 112(6):1327–34. doi:10.1097/AOG.0b013e31818c2b20 PMID:19037043

Siebers AG, Klinkhamer PJJM, Grefte JMM, Massuger LFAG, Vedder JEM, Beijers-Broos A, et al. (2009). Comparison of liquid-based cytology with conventional cytology for detection of cervical cancer precursors: a randomized controlled trial. [Erratum in: JAMA. 2009 302(21):2322] *JAMA*. 302(16):1757–64. doi:10.1001/jama.2009.1569 PMID:19861667

Sigurdsson K (2013). Is a liquid-based cytology more sensitive than a conventional Pap smear? *Cytopathology*. 24(4):254–63. doi:10.1111/cyt.12037 PMID:23331613

Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al.; Forum Group Members; Bethesda 2001 Workshop (2002). The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA*. 287(16):2114–9. doi:10.1001/jama.287.16.2114 PMID:11966386

Solomon D, Schiffman M, Tarone R; ALTS Group (2001). Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst*. 93(4):293–9. doi:10.1093/jnci/93.4.293 PMID:11181776

Somrak TM, Sorensen K, Abdul-Karim F (1990). Pap smear: collection, handling and quality assurance. Chicago (IL), USA: ASCP Press.

Spriggs AI (1977). History of cytodiagnosis. *J Clin Pathol*. 30(12):1091–102. doi:10.1136/jcp.30.12.1091 PMID:604355

Sriplung H, Singkham P, Iamsirithaworn S, Jiraphongsa C, Bilheem S (2014). Success of a cervical cancer screening program: trends in incidence in Songkhla, southern Thailand, 1989–2010, and prediction of future incidences to 2030. *Asian Pac J Cancer Prev*. 15(22):10003–8. doi:10.7314/APJCP.2014.15.22.10003 PMID:25520060

Stanczuk GA, Baxter GJ, Currie H, Forson W, Lawrence JR, Cuschieri K, et al. (2017). Defining optimal triage strategies for hrHPV screen-positive women – an evaluation of HPV 16/18 genotyping, cytology, and p16/Ki-67 cytoimmunochemistry. *Cancer Epidemiol Biomarkers Prev*. 26(11):1629–35. doi:10.1158/1055-9965.EPI-17-0534 PMID:28887297

Stoler MH, Baker E, Boyle S, Aslam S, Ridder R, Huh WK, et al. (2020). Approaches to triage optimization in HPV primary screening: extended genotyping and p16/Ki-67 dual-stained cytology – retrospective insights from ATHENA. *Int J Cancer*. 146(9):2599–607. doi:10.1002/ijc.32669 PMID:31490545

Stoler MH, Schiffman M; Atypical Squamous Cells of Undetermined Significance–Low-grade Squamous Intra-epithelial Lesion Triage Study (ALTS) Group (2001). Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. *JAMA*. 285(11):1500–5. doi:10.1001/jama.285.11.1500 PMID:11255427

Strander B, Andersson-Ellström A, Milsom I, Rådberg T, Ryd W (2007). Liquid-based cytology versus conventional Papanicolaou smear in an organized screening program: a prospective randomized study. *Cancer*. 111(5):285–91. doi:10.1002/cncr.22953 PMID:17724676

Sulik SM, Kroeger K, Schultz JK, Brown JL, Becker LA, Grant WD (2001). Are fluid-based cytologies superior to the conventional Papanicolaou test? A systematic review. *J Fam Pract*. 50(12):1040–6. PMID:11742605

Sultana F, English DR, Simpson JA, Canfell K, Gertig DM, Saville M (2014). High-grade cervical abnormalities and cervical cancer in women following a negative Pap smear with and without an endocervical component: a cohort study with 10 years of follow-up. *Int J Cancer*. 135(5):1213–9. doi:10.1002/ijc.28756 PMID:24488882

Swailes AL, Hossler CE, Kesterson JP (2019). Pathway to the Papanicolaou smear: the development of cervical cytology in twentieth-century America and implications in the present day. *Gynecol Oncol*. 154(1):3–7. doi:10.1016/j.ygyno.2019.04.004 PMID:30995961

Sykes PH, Harker DY, Miller A, Whitehead M, Neal H, Wells JE, et al. (2008). A randomised comparison of SurePath liquid-based cytology and conventional smear cytology in a colposcopy clinic setting. *BJOG*. 115(11):1375–81. doi:10.1111/j.1471-0528.2008.01865.x PMID:18823488

Talbott EO, Norman SA, Kuller LH, Ishii EK, Baffone KM, Dunn MS, et al. (1995). Refining preventive strategies for invasive cervical cancer: a population-based case-control study. *J Womens Health*. 4(4):387–95. doi:10.1089/jwh.1995.4.387

Tanabodee J, Thepsuwan K, Karalak A, Laoaree O, Krachang A, Manmatt K, et al. (2015). Comparison of efficacy in abnormal cervical cell detection between liquid-based cytology and conventional cytology. *Asian Pac J Cancer Prev*. 16(16):7381–4. doi:10.7314/APJCP.2015.16.16.7381 PMID:26514540

Tarkkanen J, Geagea A, Nieminen P, Anttila A (2003). Quality improvement project in cervical cancer screening: practical measures for monitoring laboratory performance. *Acta Obstet Gynecol Scand*. 82(1):82–8. doi:10.1034/j.1600-0412.2003.820115.x PMID:12580846

Taylor S, Kuhn L, Dupree W, Denny L, De Souza M, Wright TC Jr (2006). Direct comparison of liquid-based and conventional cytology in a South African screening trial. *Int J Cancer*. 118(4):957–62. doi:10.1002/ijc.21434 PMID:16152600

Taylor VM, Yasui Y, Burke N, Nguyen T, Acorda E, Thai H, et al. (2004). Pap testing adherence among Vietnamese American women. *Cancer Epidemiol Biomarkers Prev*. 13(4):613–9. PMID:15066927

Thangarajah F, Einzmann T, Bergauer F, Patzke J, Schmidt-Petruschkat S, Theune M, et al. (2016). Cervical screening program and the psychological impact of an abnormal Pap smear: a self-assessment questionnaire study of 590 patients. *Arch Gynecol Obstet*. 293(2):391–8. doi:10.1007/s00404-015-3821-z PMID:26202136

Theil KS (2012). Bone marrow processing and normal morphology. In: Kottke-Marchant K, Davis BH, editors. Laboratory hematology practice. 1st ed. Oxford, UK: Wiley-Blackwell; pp. 281–99. doi:10.1002/9781444398595.ch22

Thrall MJ (2019). Automated screening of Papanicolaou tests: a review of the literature. *Diagn Cytopathol*. 47(1):20–7. doi:10.1002/dc.23931 PMID:29603675

Tsoumpou I, Arbyn M, Kyrgiou M, Wentzensen N, Koliopoulos G, Martin-Hirsch P, et al. (2009). p16INK4a immunostaining in cytological and histological specimens from the uterine cervix: a systematic review and meta-analysis. *Cancer Treat Rev*. 35(3):210–20. doi:10.1016/j.ctrv.2008.10.005 PMID:19261387

UNFPA (2019). UNFPA Tajikistan. Key results of Tajikistan in 2019. United Nations Population Fund. Available from: https://www.unfpa.org/data/transparency-portal/unfpa-tajikistan.

Vaccarella S, Franceschi S, Engholm G, Lönnberg S, Khan S, Bray F (2014). 50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence. *Br J Cancer*. 111(5):965–9. doi:10.1038/bjc.2014.362 PMID:24992581

Vaccarella S, Lortet-Tieulent J, Plummer M, Franceschi S, Bray F (2013). Worldwide trends in cervical cancer incidence: impact of screening against changes in disease risk factors. *Eur J Cancer*. 49(15):3262–73. doi:10.1016/j.ejca.2013.04.024 PMID:23751569

van Ballegooijen M, Hermens R (2000). Cervical cancer screening in the Netherlands. *Eur J Cancer*. 36(17):2244–6. doi:10.1016/S0959-8049(00)00317-8 PMID:11072213

Vicus D, Sutradhar R, Lu Y, Elit L, Kupets R, Paszat L; Investigators of the Ontario Cancer Screening Research Network (2014). The association between cervical cancer screening and mortality from cervical cancer: a population based case-control study. *Gynecol Oncol*. 133(2):167–71. doi:10.1016/j.ygyno.2014.02.037 PMID:24589414

Vicus D, Sutradhar R, Lu Y, Kupets R, Paszat L; Ontario Cancer Screening Research Network (2015). Association between cervical screening and prevention of invasive cervical cancer in Ontario: a population-based case-control study. *Int J Gynecol Cancer*. 25(1):106–11. doi:10.1097/IGC.0000000000000305 PMID:25377725

Virani S, Sriplung H, Bilheem S, Sripan P, Maneesai P, Waisri N, et al. (2018). Effect of the national screening program on malignancy status of cervical cancer in northern Thailand. *Int J Public Health*. 63(3):377–85. doi:10.1007/s00038-018-1077-7 PMID:29362857

von Knebel Doeberitz M (2002). New markers for cervical dysplasia to visualise the genomic chaos created by aberrant oncogenic papillomavirus infections. *Eur J Cancer*.

38(17):2229–42. doi:10.1016/S0959-8049(02)00462-8 PMID:12441259

von Knebel Doeberitz M, Rittmüller C, zur Hausen H, Dürst M (1992). Inhibition of tumorigenicity of cervical cancer cells in nude mice by HPV E6-E7 anti-sense RNA. *Int J Cancer*. 51(5):831–4. doi:10.1002/ijc.2910510527 PMID:1319412

Wang J, Andrae B, Sundström K, Ploner A, Ström P, Elfström KM, et al. (2017). Effectiveness of cervical screening after age 60 years according to screening history: nationwide cohort study in Sweden. *PLoS Med*. 14(10):e1002414. doi:10.1371/journal.pmed.1002414 PMID:29065127

Wang J, Elfström KM, Andrae B, Nordqvist Kleppe S, Ploner A, Lei J, et al. (2020). Cervical cancer case–control audit: results from routine evaluation of a nationwide cervical screening program. *Int J Cancer*. 146(5):1230–40. doi:10.1002/ijc.32416 PMID:31107987

Wardle J, Pernet A, Stephens D (1995). Psychological consequences of positive results in cervical cancer screening. *Psychol Health*. 10(3):185–94. doi:10.1080/08870449508401948

Weiss VL, Cate F, Bloom L, Fadare O, Coogan AC, Desouki MM (2016). Age cut-off for reporting endometrial cells on a Papanicolaou test: 50 years may be more appropriate than 45 years. *Cytopathology*. 27(4):242–8. doi:10.1111/cyt.12280 PMID:26689647

Wentzensen N, Bergeron C, Cas F, Eschenbach D, Vinokurova S, von Knebel Doeberitz M (2005). Evaluation of a nuclear score for p16^{INK4a}-stained cervical squamous cells in liquid-based cytology samples. *Cancer*. 105(6):461–7. doi:10.1002/cncr.21378 PMID:16116604

Wentzensen N, Clarke MA, Bremer R, Poitras N, Tokugawa D, Goldhoff PE, et al. (2019). Clinical evaluation of human papillomavirus screening with p16/Ki-67 dual stain triage in a large organized cervical cancer screening program. *JAMA Intern Med*. 179(7):881–8. doi:10.1001/jamainternmed.2019.0306 PMID:31081870

Wentzensen N, Fetterman B, Castle PE, Schiffman M, Wood SN, Stiemerling E, et al. (2015). p16/Ki-67 dual stain cytology for detection of cervical precancer in HPV-positive women. *J Natl Cancer Inst*. 107(12):djv257. doi:10.1093/jnci/djv257 PMID:26376685

Wentzensen N, Schiffman M, Palmer T, Arbyn M (2016). Triage of HPV positive women in cervical cancer screening. *J Clin Virol*. 76(Suppl 1):S49–55. doi:10.1016/j.jcv.2015.11.015 PMID:26643050

Wentzensen N, Schwartz L, Zuna RE, Smith K, Mathews C, Gold MA, et al. (2012). Performance of p16/Ki-67 immunostaining to detect cervical cancer precursors in a colposcopy referral population. *Clin Cancer Res*. 18(15):4154–62. doi:10.1158/1078-0432.CCR-12-0270 PMID:22675168

Whitlock EP, Vesco KK, Eder M, Lin JS, Senger CA, Burda BU (2011). Liquid-based cytology and human papillomavirus testing to screen for cervical cancer: a systematic review for the U.S. Preventive Services Task Force. [Erratum in: Ann Intern Med. 2012 156(1 Pt 1):71–2] *Ann Intern Med*. 155(10):687–97, W214–5. doi:10.7326/0003-4819-155-10-201111150-00376 PMID:22006930

WHO (2019). Better noncommunicable disease outcomes: challenges and opportunities for health systems. Turkmenistan county assessment. Copenhagen, Denmark: World Health Organization Regional Office for Europe. Available from: https://www.euro.who.int/__data/assets/pdf_file/0013/403015/HSS-NCDs-TKM_WEB-1.pdf.

Wilbur DC, Black-Schaffer WS, Luff RD, Abraham KP, Kemper C, Molina JT, et al. (2009). The Becton Dickinson FocalPoint GS Imaging System: clinical trials demonstrate significantly improved sensitivity for the detection of important cervical lesions. *Am J Clin Pathol*. 132(5):767–75. doi:10.1309/AJCP8VE7AWBZCVQT PMID:19846820

Williams ARW (2006). Liquid-based cytology and conventional smears compared over two 12-month periods. *Cytopathology*. 17(2):82–5. doi:10.1111/j.1365-2303.2006.00339.x PMID:16548992

Wright TC Jr, Behrens CM, Ranger-Moore J, Rehm S, Sharma A, Stoler MH, et al. (2017). Triaging HPV-positive women with p16/Ki-67 dual-stained cytology: results from a sub-study nested into the ATHENA trial. *Gynecol Oncol*. 144(1):51–6. doi:10.1016/j.ygyno.2016.10.031 PMID:28094038

Xu L, Verdoodt F, Wentzensen N, Bergeron C, Arbyn M (2016). Triage of ASC-H: a meta-analysis of the accuracy of high-risk HPV testing and other markers to detect cervical precancer. *Cancer Cytopathol*. 124(4):261–72. doi:10.1002/cncy.21661 PMID:26618614

Yabroff KR, Saraiya M, Meissner HI, Haggstrom DA, Wideroff L, Yuan G, et al. (2009). Specialty differences in primary care physician reports of Papanicolaou test screening practices: a national survey, 2006 to 2007. *Ann Intern Med*. 151(9):602–11. doi:10.7326/0003-4819-151-9-200911030-00005 PMID:19884621

Yang B, Morrell S, Zuo Y, Roder D, Tracey E, Jelfs P (2008). A case-control study of the protective benefit of cervical screening against invasive cervical cancer in NSW women. *Cancer Causes Control*. 19(6):569–76. doi:10.1007/s10552-008-9118-9 PMID:18286380

Yang DX, Soulos PR, Davis B, Gross CP, Yu JB (2018). Impact of widespread cervical cancer screening: number of cancers prevented and changes in race-specific incidence. *Am J Clin Oncol*. 41(3):289–94. doi:10.1097/COC.0000000000000264 PMID:26808257

Yanikkerem E, Özdemir M, Bingol H, Tatar A, Karadeniz G (2009). Women's attitudes and expectations regarding gynaecological examination. *Midwifery*. 25(5):500–8. doi:10.1016/j.midw.2007.08.006 PMID:18086509

Yu CK, Rymer J (1998). Women's attitudes to and awareness of smear testing and cervical cancer. *Br J Fam Plann*. 23(4):127–33. PMID:9882766

Zappa M, Visioli CB, Ciatto S, Iossa A, Paci E, Sasieni P (2004). Lower protection of cytological screening for adenocarcinomas and shorter protection for younger women: the results of a case–control study in Florence. *Br J Cancer*. 90(9):1784–6. doi:10.1038/sj.bjc.6601754 PMID:15150597

4.4 HPV testing

4.4.1 Technical descriptions

(a)   Introduction

It has long been recognized that there is a strong etiological link between persistent infection with certain HPV types and subsequent development of cervical precancer and cancer. This has led to the idea that the detection of sequences of the HPV genome could become an alternative screening tool that could replace screening by the microscopic examination of cervical cells (IARC, 2005, 2007, 2012; Bouvard et al., 2009; see also Sections 1.2.1 and 1.2.2).

The HPV genome is a circular, double-stranded DNA molecule that codes for two late proteins (L1 and L2), which form the capsid, and several early (E) genes, which code for various proteins that are important for diverse viral functions. The E6 and E7 proteins are essential for the transformation of infected cells towards neoplasia (IARC, 2007, 2012).

Large RCTs have demonstrated that women with a negative hrHPV DNA test result have lower risks of CIN3 and cervical cancer than women with normal cervical cytology; therefore, many countries are moving towards screening with HPV tests (Arbyn et al., 2012; Huh et al., 2015; Machalek et al., 2019; Ronco et al., 2014; von Karsa et al., 2015). Currently, a multitude of hrHPV assays are available, but only a few have been clinically validated for use in cervical cancer screening against internationally agreed clinical criteria (Poljak et al., 2020). This section discusses HPV nucleic acid tests that detect DNA or RNA sequences of alpha HPV types that are considered to be carcinogenic, i.e. the 12 types classified as carcinogenic to humans (Group 1): HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. HPV68, which is probably carcinogenic to humans (Group 2A), and HPV66, which is possibly carcinogenic to humans (Group 2B), are often included in the panel of types targeted

by the hrHPV tests (Bernard et al., 2010; IARC, 2012), although their etiological fraction in cervical cancer carcinogenesis is very low and their inclusion decreases the clinical specificity of such tests (see Sections 1.2.1 and 1.2.2 and Figs. 1.9 and 1.10).

(b)   Categories of HPV nucleic acid tests

hrHPV assays can be classified by the following parameters: the nucleic acid targeted (viral genomic DNA [HPV DNA tests] or viral messenger RNA [mRNA] [HPV RNA tests]), the viral genes targeted, the level of genotyping detail, whether signal amplification (e.g. hybrid capture) or target amplification (e.g. polymerase chain reaction [PCR] or next-generation sequencing) is used, the method of identification of amplicons, the output result (qualitative or quantitative), and the inclusion of internal controls that check the validity of the specimen. An inventory of more than 200 HPV tests that were available in 2020 and are classified according to these principles is available in Poljak et al. (2020).

The main applied test systems used to identify HPV nucleic acid sequences are hybridization and PCR. In hybrid capture, RNA probes hybridize with complementary HPV DNA if present in a sample; the DNA/RNA hybrids are subsequently captured by anti-DNA/RNA antibodies coupled to an enzyme that generates a chemical reaction and yields a quantified light signal (Lorincz, 1997). In PCR systems, one or more adjacent pairs of oligonucleotide primers directed to the 3′ and 5′ ends of a target sequence will bind to it and initialize amplification of the DNA between the primers by the temperature-sensitive Taq DNA polymerase. The amplified target DNA is called an amplicon. After multiple cycles of amplification, controlled by alternating the temperature, a large number of amplicons are generated. PCRs targeting short amplicons are analytically more sensitive than those targeting a longer amplicon (Iftner & Villa, 2003). Diverse systems are used to identify the amplicons. In real-time PCR, a

quantified light signal is generated that is correlated with the amount of target DNA (Josefsson et al., 1999). Real-time PCR can also be applied in multiplex format, in which the presence of and viral load of multiple carcinogenic HPV types can be assessed simultaneously and with control of the amount of input DNA (Moberg et al., 2004).

The identification of hrHPV DNA indicates the presence of the virus, whereas the presence of hrHPV RNA may serve as an indication of viral activity, and it has therefore been proposed by some researchers to be a more specific marker of cervical neoplasia than DNA (Haedicke & Iftner, 2016).

HPV tests can target multiple sequences throughout the viral genome or specific parts of a given viral gene. Many tests target the well-conserved part of the *L1* gene, whereas others target *E* genes. Viral integration in the human genome, which often occurs in the *E2* region, results in interruption of HPV DNA and enhanced transcription of the *E6–E7* sequence, which may predispose the cell to neoplastic transformation (zur Hausen, 2002). However, this molecular pathogenetic pathway has been challenged by HPV genome-wide next-generation sequencing analyses, which indicate that integration into the host DNA can occur almost anywhere throughout the viral genome (Hu et al., 2015; Dyer et al., 2016). Moreover, no epidemiological evidence is currently available that indicates differences in diagnostic accuracy between tests targeting different genes (Arbyn et al., 2015).

With regard to the level of detail in HPV genotyping, the following can be distinguished: (i) no genotyping; (ii) limited genotyping, in which the most carcinogenic HPV types, HPV16 or HPV18 with or without HPV45, are distinguished from the other hrHPV types; (iii) extended genotyping, in which more hrHPV types – but not all – are distinguished separately; and (iv) full genotyping assays, which identify all individual hrHPV types of the high-risk group separately.

Some full genotyping tests detect additional individual HPV types that do not belong to the high-risk group. Certain types (HPV types 26, 53, 66, 67, 73, and 82) are possibly carcinogenic to humans (Group 2B). Their inclusion in HPV screening tests would increase the number of false-positive results and increase the burden of follow-up, cost, and harms associated with screening (see also Sections 1.2.1 and 1.2.2). Epidemiological research is under way to investigate whether all 12 HPV types classified as carcinogenic to humans (Group 1) should be routinely detected in primary HPV screening in an optimally efficient screening programme.

(c) Clinical applications of HPV testing

HPV tests can be used for several clinical purposes: (1) as a primary cervical cancer screening test, alone or in combination with cytology (co-testing); (2) as a triage test for women with minor abnormal cervical cytology in the context of cytology-based screening; (3) for the triage of women with a positive primary hrHPV screening test result by genotyping, or as delayed triage when the reflex triage test result is negative; and (4) to monitor the success or failure of treatment of a precancerous lesion. Triage of hrHPV-positive women (application 3), distinguishes between (i) reflex triage with genotyping, in which the detection of the most carcinogenic types (HPV16 or HPV18) triggers referral to colposcopy, leaving women who are positive only for other hrHPV types to be triaged further, and (ii) delayed triage of hrHPV-positive women who had a negative reflex HPV triage test result. Reflex triage is the immediate testing with markers using the same specimen used for primary screening. New triage strategies propose to fine-tune the management of hrHPV-positive women according to the risk of present or incipient CIN3+ associated with individual genotypes or groups of genotypes (Cheung et al., 2020; Demarco et al., 2020).

In addition to clinical purposes, HPV tests can also be used for epidemiological research and to evaluate the effects of HPV vaccination. To measure the effects of HPV vaccination in trials, high analytical sensitivity is required, whereas in clinical applications accuracy for clinically relevant outcomes is important (as discussed further below) (WHO, 2010; Dillner et al., 2011). High-grade cervical lesions including CIN2+ (in particular, CIN3+) and AIS, and cervical SCC and adenocarcinoma of the cervix are all relevant clinical outcomes (Herbert et al., 2008).

HPV tests are typically performed on cervical specimens taken by health-care workers, but they can also be performed on self-collected vaginal samples or urine and on tissue specimens. This section focuses on the use of HPV tests in cervical cancer screening using cervical samples taken by a health professional. The use of HPV testing in other settings is described elsewhere: HPV genotyping in triage of hrHPV-positive women in Section 4.4.7 and hrHPV testing on self-collected samples and the use of HPV RNA testing in Sections 4.4.5 and 4.4.6, respectively.

In primary screening, hrHPV tests should yield results that are informative about the risk of having or developing cervical precancer or cancer and should have a balanced clinical sensitivity and specificity. Infections with low concentrations of virus, in particular infections with less carcinogenic hrHPV types that usually clear spontaneously, should ideally not be detected by a screening test (Snijders et al., 2003; Eklund et al., 2014).

(i)   Principles of HPV test validation

In 2009, an international team of virologists and clinical epidemiologists defined the minimum requirements that HPV assays should fulfil for them to be accepted for use in cervical cancer screening (Meijer et al., 2009). Two tests were accepted as standard comparator tests: Hybrid Capture 2 (HC2) and GP5+/6+ PCR enzyme immunoassay (EIA). Four large

population-based RCTs, conducted in Europe, have provided consistent evidence that screening with these assays provides better protection against future CIN3 or cancer compared with good-quality cytology (Arbyn et al., 2012; Ronco et al., 2014). However, to validate other hrHPV DNA assays, it is not required to set up RCTs with long-term follow-up. It is deemed sufficient that three criteria (Table 4.21) are fulfilled to accept another hrHPV DNA test for use in primary cervical cancer screening. The given hrHPV DNA test (the index test) should have non-inferior cross-sectional sensitivity and specificity for CIN2+ compared with one of the comparator assays (HC2 or GP5+/6+ PCR EIA) (Meijer et al., 2009). The agreed benchmarks (index test divided by standard comparator test) are 0.90 for relative sensitivity and 0.98 for relative specificity. The paired statistical test for non-inferiority will be significant when the lower bound of the 90% confidence interval around the relative sensitivity or relative specificity is greater than or equal to the benchmark (Tang et al., 2003). A representative set of cervical samples (at least 60 CIN2+ cases and at least 800 < CIN2 cases) derived from a population-based screening cohort should be selected (Meijer et al., 2009). Moreover, the new test should show high intralaboratory and interlaboratory reproducibility, with a lower bound of the 95% confidence interval of at least 87% or a kappa of at least 0.5 (Meijer et al., 2009). The recommended sample size for the reproducibility assessment is at least 500 with an hrHPV prevalence of 30% as established with a standard comparator test (Table 4.21). These guidelines apply only to hrHPV DNA testing. For screening tests using targets other than hrHPV DNA (e.g. HPV RNA, methylation markers, protein markers, or other test systems), additional longitudinal criteria are needed. For HPV DNA tests, these longitudinal data are not needed because the longitudinal safety (low 5-year risk of cancer after an earlier negative test result) is established through RCTs and supported by observational

Table 4.21 International validation criteria for high-risk human papillomavirus (hrHPV) DNA tests acceptable for use in primary cervical cancer screening, based on the relative accuracy for detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) of an index HPV test compared with a standard comparator test[a]

Criteria	Study population needed	Target
1. Relative sensitivity[b]	≥ 60 samples from women with CIN2+	*P* for non-inferiority < 0.05[c] (accepting 0.90 as benchmark) The lower bound of the 90% CI should be ≥ 0.90
2. Relative specificity[b]	≥ 800 samples from women with < CIN2	*P* for non-inferiority < 0.05[c] (accepting 0.98 as benchmark) The lower bound of the 90% CI should be ≥ 0.98
3. Intralaboratory and interlaboratory reproducibility	≥ 500 samples from a screening population with an hrHPV prevalence of 30% (as established with a standard comparator test)	Lower bound of the 95% CI ≥ 87% Kappa ≥ 0.5

CI, confidence interval; CIN2, cervical intraepithelial neoplasia grade 2; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; hrHPV, high-risk human papillomavirus.

[a] Standard comparator tests: Hybrid Capture 2 and GP5+/6+ polymerase chain reaction (PCR) enzyme immunoassay (EIA). These two tests have been validated through randomized controlled trials that demonstrated lower incidence of cervical cancer compared with good-quality cytology.

[b] Relative accuracy of the index hrHPV DNA test compared with the standard comparator test for the outcome CIN2+.

[c] One-sided non-inferiority test for paired data accepting a power of 90% and a confidence level of 95% (Tang et al., 2003). Because this statistical test is one-sided, the equivalent confidence level for the lower bound of the CI (two-sided expression) should be 90%.

Compiled from Meijer et al. (2009).

longitudinal studies. However, for other molecular targets, a high cross-sectional sensitivity does not provide sufficient evidence that the lead-time gain (time span between detectability of a neoplastic lesion and when it becomes clinically manifest) is similar to that for HPV DNA and that use of the same screening interval as that proposed for hrHPV DNA screening tests (usually 5 years or longer) can be accepted as safe.

(ii) Updating and extension of HPV test validation guidelines

The international validation criteria (Meijer et al., 2009) are for hrHPV DNA testing on cervical samples. Currently, new criteria are being developed that will include HPV genotyping and HPV testing on alternative specimens (self-collected vaginal samples or urine) and may involve standard comparator tests other than HC2 and GP5+/6+ PCR EIA (Arbyn & Hillemanns, 2018). Recent meta-analyses indicated that HPV tests based on a principle of signal amplification (e.g. HC2 or *care*HPV) are less sensitive and specific for the detection of CIN2+ on self-collected vaginal samples than on clinician-collected cervical samples. RNA-based HPV assays are less sensitive on self-collected samples. However, PCR-based hrHPV DNA assays, validated on cervical specimens, seem to be as sensitive and nearly as specific on vaginal samples as they are on cervical samples (Arbyn et al., 2014, 2018).

(iii) Assays that detect molecules other than hrHPV DNA

An HPV RNA assay targeting E6/E7 transcripts of only five HPV types (HPV types 16, 18, 31, 33, and 45) was significantly less sensitive but more specific than the standard comparator hrHPV DNA tests (Arbyn et al., 2015). Another RNA HPV assay targeting E6/E7 transcripts of 14 hrHPV types in bulk fulfils the three international cross-sectional validation criteria described in Table 4.21 (Arbyn et al., 2015). The assessment of its longitudinal performance and risk of CIN3+ after baseline testing with an RNA

test versus after testing with a validated DNA test is covered in Section 4.4.6.

(iv) Other important factors that influence the choice of a screening test

In addition to accuracy, other characteristics need to be taken into account when choosing a screening test, such as the availability of the assay, reagents, and disposables, the throughput capacity and turnaround time (time span between arrival of the specimen and communication of the result), costs, applicability on samples taken by the woman (self-collected vaginal samples or urine), the requirement for equipped laboratories, user-friendliness, the need for running water and electricity, the possibility of point-of-care testing, and the possibility of providing triage information (genotyping or viral load). A comprehensive overview of logistic, regulatory, managerial, training, and quality control aspects of the choice of HPV assays, procurement, sample collection, transport of specimens to the laboratory, pre-analytical handling, testing, and result communication was given in a recent WHO document (WHO, 2020a).

Most of the assays that have been validated to date for screening require a well-equipped laboratory to perform the HPV tests. Two hrHPV DNA assays, one using the hybrid capture principle and the other using a cartridge, are prequalified by WHO for hrHPV testing in field conditions in low-resource countries (WHO, 2019). Point-of-care hrHPV testing is particularly relevant for screen-and-treat strategies (see Section 5.1).

4.4.2 Comparison of HPV DNA testing versus cytology

(a) Introduction

The evidence for HPV DNA testing as a modality for primary cervical screening has been accumulating for two decades. From first principles, molecular testing for the presence of HPV

provides a sensitive assessment of a woman's risk of currently harbouring, or in the future developing, a precancer or invasive cervical cancer, because nearly all cervical cancers are caused by HPV infection.

In the 2005 *IARC Handbook* on cervical cancer screening (IARC, 2005), the performance of HPV assays in the detection of precancerous lesions was compared with that of cytology. At the time, almost all of the evidence was from cross-sectional studies, and there was no prospective evaluation of the impact of primary HPV screening on invasive cervical cancer. Nevertheless, the *Handbook* concluded: "For primary screening of women older than 30 years of age, HPV testing yields on average about 10–20% greater sensitivity and 10% lower specificity than cytology (either conventional or liquid-based). In some studies, the combination of cytology and HPV testing (as independent or reflex testing) attained very high sensitivity and negative predictive values (approaching 100%). A testing combination with such a high negative predictive value could potentially allow screening intervals to be increased, e.g., from the minimum of three years up to five years or longer, depending on the population and risk profile. The drawback of this approach is the loss in specificity with respect to either test in isolation due to the excessive number of patients who would need to be referred for colposcopy."

Since the publication of the 2005 *IARC Handbook*, the evidence base on the sensitivity and NPV of HPV DNA testing versus cytology has become substantially larger, and direct evidence has become available on the protection provided by HPV-based and cytology-based screening against cervical cancer and death from cervical cancer. Furthermore, the screening process for CIN2+ and CIN3+ has been evaluated in the context of a combination of measures taken to increase specificity and minimize harms, including the appropriate use of triage of HPV-positive women (see Section 4.4.7 and

Section 4.4.8). The evidence base for the relative performance of HPV and cytology screening now includes: (i) cross-sectional diagnostic studies, which have been synthesized in meta-analyses to provide evidence on the relative sensitivity and specificity of HPV DNA testing versus cytology for the detection of CIN2 and CIN3; (ii) evidence from longitudinal RCTs, mainly in high-income countries, to evaluate whether the increased detection of CIN2+ with HPV testing results in a decrease in CIN2+ in the subsequent screening round; (iii) evidence from a major RCT of HPV DNA testing versus cytology versus VIA screening in India, with cervical cancer incidence and mortality outcomes, and evidence from individual data of four RCTs in Europe that were pooled to evaluate the effect on cancer incidence; (iv) randomized health services trials and national, regional, and pilot screening programmes, which provide information about the impact of HPV-based screening, sometimes with new, less-aggressive protocols, on the detection of CIN3+ and on resource consumption, and which will provide evidence about effectiveness, and (v) longitudinal studies of women screened by HPV testing and cytology, which are particularly relevant for defining risk-based screening intervals.

This experience, combined with well-validated modelling of the longer-term effects of scaled-up HPV testing, has supported the increased use of HPV testing as the sole primary screening test (or, in a few settings, as a co-test with cytology) in high-income countries and the recommendation to support HPV testing in the 2020 WHO strategic plan for the elimination of cervical cancer as a public health problem (WHO, 2020b). Since 2017, several high-income countries have transitioned from cytology screening to primary HPV screening programmes at screening intervals of 5 years or longer, and this is increasingly also providing evidence on the real-world experience with HPV screening.

(b)   Diagnostic studies

A Cochrane review published in 2017 compared the accuracy of HPV testing and cervical cytology for the detection of CIN2+ and CIN3+ in women who were participating in cervical cancer screening and who were not being followed up for previous cytological abnormalities (Koliopoulos et al., 2017). This systematic review and meta-analysis searched for articles published between 1992 and 2015. The review focused on studies in which all women received both HPV testing and cervical cytology. A combination of colposcopy and histology was used as the reference standard. If at least one of the screening tests was positive, women underwent colposcopy with directed biopsy of abnormal areas and histological verification. Women did not know their disease status at the time of recruitment. Of the 40 eligible studies, which included more than 140 000 women, 29 studies conducted head-to-head comparison of HPV DNA testing by signal amplification or target amplification versus conventional cytology or LBC (Pap) testing using a threshold of ASC-US for the detection of CIN2+ or CIN3+.

For the detection of CIN2+, the sensitivity of HPV DNA-based tests was higher than that of cytology methods (pooled relative sensitivity, 1.35; 95% CI, 1.23–1.48) and the specificity was lower (pooled relative specificity, 0.94; 95% CI, 0.93–0.96) (Fig. 4.2). For the detection of CIN3+, the pooled relative sensitivity was 1.37 (95% CI, 1.20–1.55) and the pooled relative specificity was 0.95 (95% CI, 0.94–0.97) (Fig. 4.3).

(c)   RCTs

(i)   Description

When the 2005 *IARC Handbook* was published, large RCTs of HPV testing in primary cervical cancer screening were in progress but had not yet reported longitudinal outcomes. Since then, eight major RCTs comparing HPV DNA-based screening with cytology-based

Fig. 4.2 Relative sensitivity (left) and relative specificity (right) of hrHPV testing compared with cytology at a threshold of ASC-US+ for the detection of CIN2+

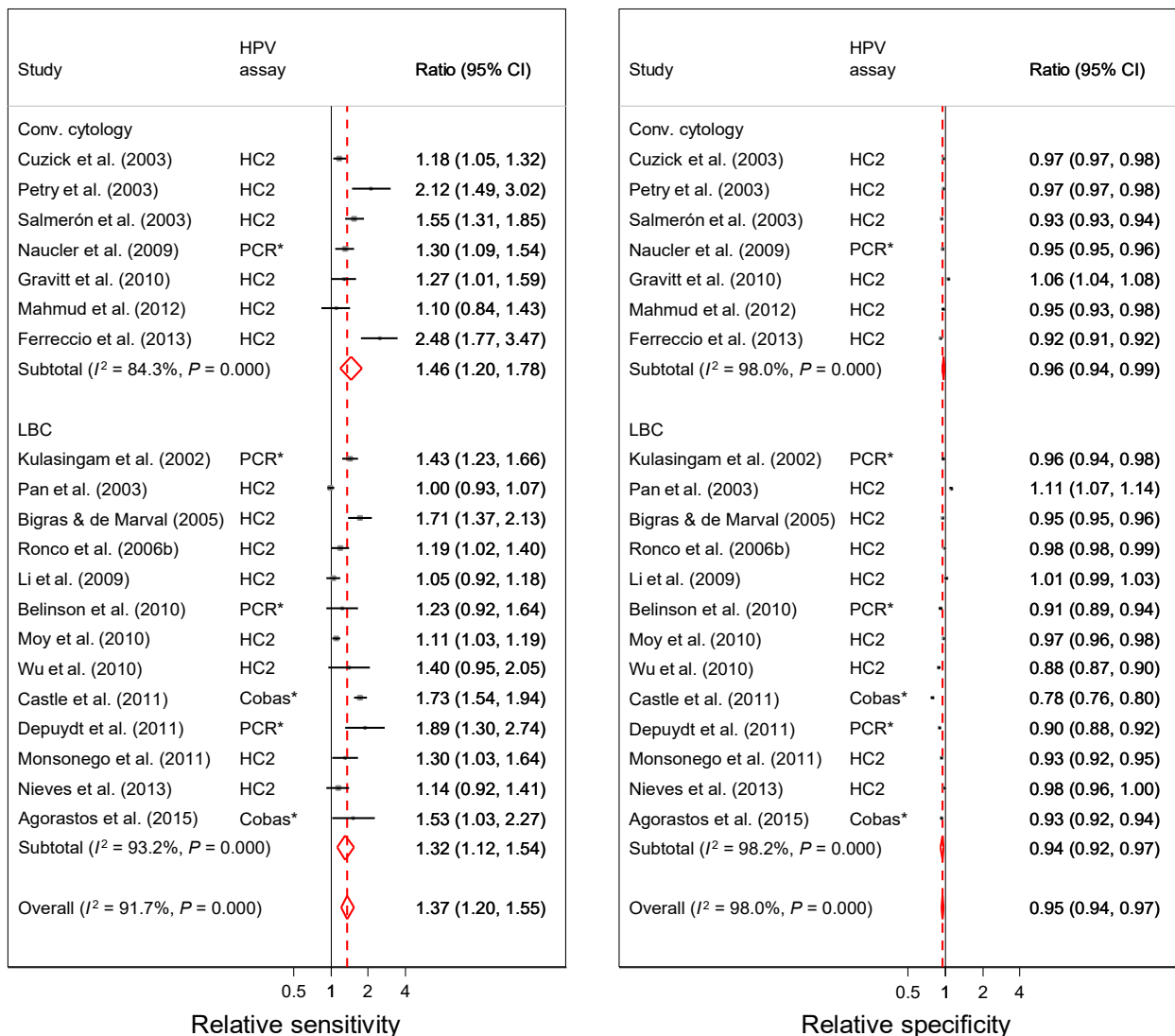| Study	HPV assay	Ratio (95% CI)
Conv. cytology		
Clavel et al. (2001)	HC2	1.47 (1.21, 1.79)
Cuzick et al. (2003)	HC2	1.16 (1.05, 1.28)
Petry et al. (2003)	HC2	2.25 (1.61, 3.14)
Salmerón et al. (2003)	HC2	1.57 (1.32, 1.86)
de Cremoux et al. (2003)	HC2	0.97 (0.84, 1.12)
Agorastos et al. (2005)	PCR*	1.50 (0.48, 4.65)
Cárdenas-Turanzas et al. (2008)	HC2	1.57 (0.82, 3.00)
Naucler et al. (2009)	PCR*	1.34 (1.16, 1.54)
Gravitt et al. (2010)	HC2	1.31 (0.92, 1.86)
Hovland et al. (2010)	PCR*	1.48 (1.03, 2.13)
Mahmud et al. (2012)	HC2	1.11 (0.87, 1.42)
Ferreccio et al. (2013)	HC2	2.76 (2.08, 3.65)
Subtotal (I^2 = 86.9%, P = 0.000)		1.45 (1.21, 1.73)
LBC		
Clavel et al. (2001)	HC2	1.14 (1.05, 1.24)
Belinson et al. (2003)	HC2	1.10 (1.05, 1.14)
Pan et al. (2003)	HC2	1.01 (0.94, 1.09)
de Cremoux et al. (2003)	HC2	1.06 (0.89, 1.27)
Bigras & de Marval (2005)	HC2	1.67 (1.38, 2.01)
Ronco et al. (2006b)	HC2	1.32 (1.14, 1.52)
Li et al. (2009)	HC2	0.97 (0.88, 1.07)
Belinson et al. (2010)	PCR*	1.47 (1.10, 1.97)
Hovland et al. (2010)	PCR*	1.35 (0.98, 1.85)
Moy et al. (2010)	HC2	1.17 (1.09, 1.25)
Wu et al. (2010)	HC2	1.33 (0.99, 1.80)
Castle et al. (2011)	Cobas*	1.71 (1.55, 1.89)
Depuydt et al. (2011)	PCR*	1.63 (1.27, 2.09)
Monsonego et al. (2011)	HC2	1.40 (1.22, 1.60)
Agorastos et al. (2015)	Cobas*	1.84 (1.39, 2.45)
Subtotal (I^2 = 93.2%, P = 0.000)		1.30 (1.16, 1.45)
Overall (I^2 = 91.9%, P = 0.000)		1.35 (1.23, 1.48)

Relative sensitivity

Study	HPV assay	Ratio (95% CI)
Conv. cytology		
Clavel et al. (2001)	HC2	0.90 (0.89, 0.91)
Cuzick et al. (2003)	HC2	0.97 (0.97, 0.98)
Petry et al. (2003)	HC2	0.97 (0.97, 0.98)
Salmerón et al. (2003)	HC2	0.94 (0.93, 0.94)
de Cremoux et al. (2003)	HC2	0.86 (0.84, 0.89)
Agorastos et al. (2005)	PCR*	0.99 (0.98, 1.00)
Cárdenas-Turanzas et al. (2008)	HC2	1.00 (0.97, 1.02)
Naucler et al. (2009)	PCR*	0.95 (0.95, 0.96)
Gravitt et al. (2010)	HC2	1.06 (1.04, 1.08)
Hovland et al. (2010)	PCR*	0.89 (0.85, 0.94)
Mahmud et al. (2012)	HC2	0.95 (0.93, 0.98)
Ferreccio et al. (2013)	HC2	0.92 (0.91, 0.93)
Subtotal (I^2 = 97.6%, P = 0.000)		0.95 (0.93, 0.97)
LBC		
Clavel et al. (2001)	HC2	0.92 (0.91, 0.94)
Belinson et al. (2003)	HC2	0.98 (0.97, 1.00)
Pan et al. (2003)	HC2	1.11 (1.08, 1.14)
de Cremoux et al. (2003)	HC2	0.89 (0.87, 0.92)
Bigras & de Marval (2005)	HC2	0.95 (0.95, 0.96)
Ronco et al. (2006b)	HC2	0.98 (0.98, 0.99)
Li et al. (2009)	HC2	1.01 (0.99, 1.03)
Belinson et al. (2010)	PCR*	0.92 (0.89, 0.95)
Hovland et al. (2010)	PCR*	0.89 (0.84, 0.93)
Moy et al. (2010)	HC2	0.97 (0.96, 0.98)
Wu et al. (2010)	HC2	0.89 (0.87, 0.90)
Castle et al. (2011)	Cobas*	0.79 (0.77, 0.81)
Depuydt et al. (2011)	PCR*	0.90 (0.88, 0.92)
Monsonego et al. (2011)	HC2	0.94 (0.93, 0.95)
Agorastos et al. (2015)	Cobas*	0.93 (0.92, 0.94)
Subtotal (I^2 = 98.0%, P = 0.000)		0.94 (0.91, 0.96)
Overall (I^2 = 97.8%, P = 0.000)		0.94 (0.93, 0.96)

Relative specificity

ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; Cobas*, cobas 4800; Conv., conventional; HC2, Hybrid Capture 2; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology; PCR*, polymerase chain reaction-based assay targeting at least 13 carcinogenic HPV types.
Created by the Working Group with data from Koliopoulos et al. (2017).

Fig. 4.3 Relative sensitivity (left) and relative specificity (right) of hrHPV testing compared with cytology at a threshold of ASC-US+ for the detection of CIN3+

Study	HPV assay	Ratio (95% CI)
Conv. cytology		
Cuzick et al. (2003)	HC2	1.18 (1.05, 1.32)
Petry et al. (2003)	HC2	2.12 (1.49, 3.02)
Salmerón et al. (2003)	HC2	1.55 (1.31, 1.85)
Naucler et al. (2009)	PCR*	1.30 (1.09, 1.54)
Gravitt et al. (2010)	HC2	1.27 (1.01, 1.59)
Mahmud et al. (2012)	HC2	1.10 (0.84, 1.43)
Ferreccio et al. (2013)	HC2	2.48 (1.77, 3.47)
Subtotal (I^2 = 84.3%, P = 0.000)		1.46 (1.20, 1.78)
LBC		
Kulasingam et al. (2002)	PCR*	1.43 (1.23, 1.66)
Pan et al. (2003)	HC2	1.00 (0.93, 1.07)
Bigras & de Marval (2005)	HC2	1.71 (1.37, 2.13)
Ronco et al. (2006b)	HC2	1.19 (1.02, 1.40)
Li et al. (2009)	HC2	1.05 (0.92, 1.18)
Belinson et al. (2010)	PCR*	1.23 (0.92, 1.64)
Moy et al. (2010)	HC2	1.11 (1.03, 1.19)
Wu et al. (2010)	HC2	1.40 (0.95, 2.05)
Castle et al. (2011)	Cobas*	1.73 (1.54, 1.94)
Depuydt et al. (2011)	PCR*	1.89 (1.30, 2.74)
Monsonego et al. (2011)	HC2	1.30 (1.03, 1.64)
Nieves et al. (2013)	HC2	1.14 (0.92, 1.41)
Agorastos et al. (2015)	Cobas*	1.53 (1.03, 2.27)
Subtotal (I^2 = 93.2%, P = 0.000)		1.32 (1.12, 1.54)
Overall (I^2 = 91.7%, P = 0.000)		1.37 (1.20, 1.55)

Relative sensitivity

Study	HPV assay	Ratio (95% CI)
Conv. cytology		
Cuzick et al. (2003)	HC2	0.97 (0.97, 0.98)
Petry et al. (2003)	HC2	0.97 (0.97, 0.98)
Salmerón et al. (2003)	HC2	0.93 (0.93, 0.94)
Naucler et al. (2009)	PCR*	0.95 (0.95, 0.96)
Gravitt et al. (2010)	HC2	1.06 (1.04, 1.08)
Mahmud et al. (2012)	HC2	0.95 (0.93, 0.98)
Ferreccio et al. (2013)	HC2	0.92 (0.91, 0.92)
Subtotal (I^2 = 98.0%, P = 0.000)		0.96 (0.94, 0.99)
LBC		
Kulasingam et al. (2002)	PCR*	0.96 (0.94, 0.98)
Pan et al. (2003)	HC2	1.11 (1.07, 1.14)
Bigras & de Marval (2005)	HC2	0.95 (0.95, 0.96)
Ronco et al. (2006b)	HC2	0.98 (0.98, 0.99)
Li et al. (2009)	HC2	1.01 (0.99, 1.03)
Belinson et al. (2010)	PCR*	0.91 (0.89, 0.94)
Moy et al. (2010)	HC2	0.97 (0.96, 0.98)
Wu et al. (2010)	HC2	0.88 (0.87, 0.90)
Castle et al. (2011)	Cobas*	0.78 (0.76, 0.80)
Depuydt et al. (2011)	PCR*	0.90 (0.88, 0.92)
Monsonego et al. (2011)	HC2	0.93 (0.92, 0.95)
Nieves et al. (2013)	HC2	0.98 (0.96, 1.00)
Agorastos et al. (2015)	Cobas*	0.93 (0.92, 0.94)
Subtotal (I^2 = 98.2%, P = 0.000)		0.94 (0.92, 0.97)
Overall (I^2 = 98.0%, P = 0.000)		0.95 (0.94, 0.97)

Relative specificity

ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; Cobas*, cobas 4800; Conv., conventional; HC2, Hybrid Capture 2; hrHPV, high-risk human papillomavirus; LBC, liquid-based cytology; PCR*, polymerase chain reaction-based assay targeting at least 13 carcinogenic HPV types.
Created by the Working Group with data from Koliopoulos et al. (2017).

screening have reported results. An important goal of the RCTs was to evaluate whether the excess CIN2+ detected by HPV DNA-based screening represented clinically relevant persistent disease. For this purpose, women were randomly assigned to HPV DNA-based testing or cytology-based screening at enrolment, and it was investigated whether an increase in detection of CIN2+ in the intervention arm versus the control arm in the first round was followed by a decrease in the second round. In addition, to avoid bias, in the second round in most studies the same screening methodology was applied in both arms. RCTs have also been used to study the benefits of combined HPV DNA testing and cytology (co-testing) compared with primary HPV DNA testing. Those analyses are reviewed in Section 4.4.4. Brief descriptions of the characteristics of the eight major RCTs are given here.

Five RCTs were conducted in European countries, all within organized screening programmes in which the target population was actively invited to primary screening and, if needed, triage testing and treatment. These programmes routinely recorded the numbers of women invited, screened, and treated.

The New Technologies for Cervical Cancer Screening (NTCC) trial was conducted at nine participating centres in Italy and enrolled a total of 94 370 women aged 25–60 years over two implementation phases in 2002–2004. In the intervention arm, co-testing with HPV (HC2) testing and LBC was applied in the first phase (45 174 women enrolled in 2002–2003) and stand-alone HPV testing was applied in the second phase (49 196 women enrolled in 2002–2004). In the first phase, participants in the intervention arm younger than 35 years were referred for colposcopy if they were ASC-US+ or if they were HPV-positive and/or ASC-US+ after 1 year. Women aged 35 years and older were referred for colposcopy if they were HPV-positive and/or ASC-US+. In the second phase, all HPV-positive women were immediately referred for colposcopy, irrespective of

age. In the control arm, women were screened using conventional cytology alone. In the second round, all women were screened using conventional cytology, and no further HPV testing was done. Results from the first two rounds of screening, with a 3-year interval (total follow-up period, 7 years), have been published (Ronco et al., 2006a, b, 2008, 2010).

The Population Based Screening Study Amsterdam (POBASCAM) trial was conducted in the Greater Amsterdam region in the Netherlands. Women aged 29–61 years were recruited in 1999–2002. A total of 44 102 women were enrolled and randomized either to co-testing with HPV DNA (GP5+/6+ PCR EIA) testing and conventional cytology or to stand-alone conventional cytology in the first round. In the second round in both arms, HPV testing and cytology were performed on all participants 5 years later. Women with HSIL cytology were immediately referred for colposcopy, and women with ASC-US or LSIL cytology were offered repeat testing after 6 months and 18 months and then referred for colposcopy if they were cytology-positive. In the intervention arm, HPV-positive women with NILM cytology were also offered repeat testing followed by colposcopy if the second HPV test was positive (Bulkmans et al., 2004). Data were initially published on the first two screening rounds, with a 5-year interval, for about half of the cohort (Bulkmans et al., 2007) and then for the entire cohort (Rijkaart et al., 2012a). Further analyses have examined long-term risks (Dijkstra et al., 2016) and additional specific hypotheses on management of different screening results with different combinations of test results over one or two screening rounds (Veldhuijzen et al., 2017; Polman et al., 2019a).

The Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Cancer Screening (SwedeScreen) trial was conducted in five cities in Sweden. A total of 12 527 women aged 32–38 years were enrolled and randomized either to co-testing with HPV

DNA (GP5+/6+ PCR EIA) testing and conventional cytology or to conventional cytology alone (Naucler et al., 2007). Women with ASC-US+ were referred for colposcopy. In the intervention arm, HPV-positive women with NILM cytology received repeat HPV testing after 12 months and were referred for colposcopy if the HPV test result was positive. In the second screening round, all women were screened with conventional cytology. The initial analysis included two screening rounds with an average of 4 years of follow-up per woman. Subsequent analyses have included long-term follow-up data (Elfström et al., 2014; Elfgren et al., 2017).

The A Randomised Trial In Screening To Improve Cytology (ARTISTIC) trial was conducted in Greater Manchester, United Kingdom. A total of 24 510 women aged 20–64 years were enrolled in 2001–2003. Women were randomized 3:1 either to co-testing with HPV DNA (HC2) testing and LBC or to LBC alone. The management of screen-positive women in both arms was similar to that in the POBASCAM trial. The screening protocol for the second round was the same as that for the first round. Data from the first two screening rounds, 3 years apart, were initially reported (Kitchener et al., 2009a, b). Further analyses have reported on the long-term follow-up of this trial (Kitchener et al., 2011).

The Finnish trial was conducted in Finland in 2003–2008 (Leinonen et al., 2012) and enrolled 132 194 women aged 25–65 years. Participants were randomized either to primary screening with HPV DNA (HC2) testing, with conventional cytology triage if HPV-positive (intervention arm) or to conventional cytology alone (control arm). The follow-up period was limited to one screening round with follow-up after 5 years for cumulative detection of CIN, AIS, and invasive cervical cancer. Women in the intervention arm who were HPV-positive and with LSIL or worse (LSIL+) cytology and women in the control arm who were LSIL+ were referred for colposcopy,

and women who were HPV-positive and with less than LSIL cytology (intervention arm) or with ASC-US (control arm) were followed up with repeat testing.

The HPV For Cervical Cancer Screening (HPV FOCAL) trial was conducted in Canada in 2008–2016 (Ogilvie et al., 2017, 2018; Coldman et al., 2020). A total of 19 009 women aged 25–65 years attending routine screening were randomized 1:1:1 into one of three groups: primary HPV DNA screening (stand-alone) with LBC triage of HPV-positive women (intervention arm), primary HPV DNA screening (stand-alone) with LBC triage of HPV-positive women and a 2-year safety check (safety arm), and LBC screening with HPV DNA triage of women with an ASC-US result (control arm) and colposcopy for women with LSIL+. In the intervention arm, HPV-negative women were recalled for exit screening with both LBC and HPV testing at 4 years. In the safety arm, HPV-negative women were recalled for exit screening with LBC at 2 years. In the control arm, women with NILM LBC were recalled for screening with LBC at 2 years and then again for exit screening with both LBC and HPV testing at 4 years.

The Hong Kong Special Administrative Region (Hong Kong SAR) trial was conducted at seven clinics in Hong Kong SAR, China, in 2010–2014 (Chan et al., 2020). A total of 15 955 women aged 30–60 years attending routine screening were randomized either to co-testing with HPV testing and LBC (intervention arm) or to LBC with HPV DNA triage of women with an ASC-US+ result (control arm). Women were referred for colposcopy if they were HPV-positive and/or had LSIL+. If the co-testing result was HPV-negative and ASC-US, repeat testing was offered. There were two rounds of screening, with a 3-year interval, and all women were screened with LBC in the second round.

The Compass trial, in Australia, is the first prospective RCT of primary HPV screening compared with cytology to be conducted in a

population with high coverage of HPV vaccination. Women aged 25–64 years were enrolled in 2015–2019 (Canfell et al., 2018). Participants were randomized 1:2 either to 2.5-yearly LBC with HPV triage of low-grade LBC (control arm) or to 5-yearly primary HPV testing (intervention arm). In the intervention arm, women who are positive for HPV16 or HPV18 are directly referred for colposcopy, and women who are positive for other (non-HPV16/18) carcinogenic HPV types undergo secondary randomization 1:1 to either LBC or dual-stain cytology (p16^{INK4a} and Ki-67). In addition, 10% of women in the intervention arm who test negative for HPV will be recalled at 2.5 years for screening with LBC, for safety monitoring purposes. To date, data on the baseline and 12-month follow-up in 4995 women enrolled in 2013–2014 in the Compass pilot trial have been published (Canfell et al., 2017).

The only RCT to evaluate the effect of a single round of screening on cervical cancer incidence and associated mortality was conducted in Osmanabad District in India. This cluster RCT included 131 746 women aged 30–59 years from 52 village clusters randomly assigned to four groups in 2000–2003 (Sankaranarayanan et al., 2009). The groups were randomly assigned to undergo screening with HPV testing (34 126 women), conventional cytology (32 058 women), or VIA (34 074 women) or to receive standard care without screening (31 488 women; control group). Women who had positive results on screening underwent colposcopy and directed biopsies, and those with cervical precancerous lesions or cancer received appropriate treatment. The main results were reported with follow-up until 2007.

Efficacy results from RCTs comparing HPV-based screening with cytology-based screening have been compiled in systematic reviews and meta-analyses (Arbyn et al., 2012; Melnikow et al., 2018). Results per trial are presented in Table 4.22 and in Fig. 4.4. Relative risks and 95% confidence intervals were recalculated by the Working Group. A normal distribution for the logarithm of the estimated relative risk was used to calculate confidence intervals. The NTCC first phase and second phase were pooled, and only NTCC participants aged 35 years and older were included in the analyses. Pooled meta-analytic estimates of the relative risks were calculated by the Working Group assuming a random-effects model and applying restricted maximum-likelihood estimation.

(ii) Detection of CIN2+ and CIN3+

In the eight RCTs comparing primary HPV DNA testing alone or co-testing with HPV DNA testing and cytology (intervention arm) with cytology (control arm), there was consistent evidence that the detection rates of CIN2+ and CIN3+ were higher in the HPV DNA testing arm than in the cytology arm in the first round of screening (Fig. 4.4). In the eight RCTs, the relative risk for the detection of CIN2+ by HPV DNA testing compared with cytology ranged from 1.13 (95% CI, 0.94–1.37) in the ARTISTIC trial (Kitchener et al., 2009b) to 10.95 (95% CI, 1.51–79.34) in the Compass trial (Canfell et al., 2017), and the relative risk for the detection of CIN3+ ranged from 0.97 (95% CI, 0.75–1.25) in the ARTISTIC trial (Kitchener et al., 2009b) to 7.46 (95% CI, 1.02–54.66) in the Compass pilot trial (Canfell et al., 2017). Although the relative risks shown in Fig. 4.4 varied considerably across studies, seven of the eight RCTs reported a relative risk for the detection of CIN2+ with a lower bound of the 95% confidence interval between 1 and 2, and five of the eight RCTs reported a relative risk for the detection of CIN3+ with a lower bound of the 95% confidence interval between 1 and 2.

The risk of CIN2+ in the second round of screening was significantly lower in women who were randomized to HPV testing than in those in the cytology arm in the first round of screening (Fig. 4.4). The relative risk of CIN2+ ranged from

Table 4.22 Randomized controlled trials with an HPV-based screening arm (intervention arm) and a cytology arm (control arm)

Trial Country Reference	Age (years)	No. of screening rounds (interval, years)	Screening strategy in round 1: intervention vs control	No. of women in round 1	No. of colposcopy referrals (%)	No. detected (%) CIN2+	No. detected (%) CIN3+	PPV for CIN3+ (%)	No. of women for round 2 calculation	No. detected (%) CIN2+	No. detected (%) CIN3+
NTCC Italy Ronco et al. (2006b, 2008, 2010)	35–60	2 (3)	Co-testing (phase 1) or hrHPV (phase 2)	34 430	2768 (8.0%)	213 (0.6%)	105 (0.3%)	3.8	33 733	16 (0.05%)	8 (0.02%)
			Cytology	34 405	928 (2.7%)	110 (0.3%)	56 (0.2%)	6.0	34 202	39 (0.1%)	26 (0.08%)
SwedeScreen Sweden Naucler et al. (2007)	32–38	2 (3)	Co-testing	6257	265 (4.2%)	114 (1.8%)	72 (1.2%)	27.2	6257	25 (0.4%)	16 (0.3%)
			Cytology	6270	150 (2.4%)	76 (1.1%)	55 (0.9%)	36.7	6270	43 (0.7%)	30 (0.5%)
ARTISTIC United Kingdom Kitchener et al. (2009a)	20–64	2 (3)	Co-testing	18 386	1247 (6.8%)	453 (2.5%)	233 (1.3%)	18.7	11 676	65 (0.6%)	29 (0.3%)
			Cytology	6124	320 (5.2%)	133 (2.2%)	80 (1.3%)	25.0	3866	34 (0.9%)	18 (0.5%)
Finnish Finland Leinonen et al. (2012)	25–65	1 (5)	hrHPV	66 410	NR	540 (0.8%)	195 (0.3%)	NR	NR	NR	NR
			Cytology	65 784	NR	319 (0.5%)	118 (0.2%)	NR	NR	NR	NR
POBASCAM Netherlands Rijkaart et al. (2012a)	29–56	2 (5)	Co-testing	19 999	NR	267 (1.3%)	171 (0.9%)	NR	19 579	160 (0.8%)	88 (0.5%)
			Cytology	20 106	NR	215 (1.1%)	150 (0.7%)	NR	19 731	184 (0.9%)	122 (0.6%)
Compass Australia Canfell et al. (2017)	25–64	1 (5)	hrHPV	4000	154 (3.8%)	44 (1.1%)	30 (0.8%)	19.5	NR	NR	NR
			Cytology	995	27 (2.7%)	1 (0.1%)	1 (0.1%)	3.7	NR	NR	NR
HPV FOCAL Canada Ogilvie et al. (2018)	25–65	2 (4)	hrHPV	9540	544 (5.7%)	147 (1.5%)	67 (0.7%)	12.3	9540	48 (0.5%)	22 (0.2%)
			Cytology	9408	290 (3.1%)	90 (9.6%)	41 (0.4%)	14.1	9408	100 (1.1%)	52 (0.6%)
Hong Kong Special Administrative Region trial China Chan et al. (2020)	30–60	2 (3)	Co-testing	7931	738 (9.3%)	75 (1.0%)	49 (0.6%)	6.6	6018	5 (0.08%)	4 (0.07%)
			Cytology	7927	157 (2.0%)	30 (0.4%)	16 (0.2%)	10.2	6203	22 (0.4%)	15 (0.2%)

ARTISTIC, A Randomised Trial In Screening To Improve Cytology; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; HPV FOCAL, HPV For Cervical Cancer Screening; NR, not reported; NTCC, New Technologies for Cervical Cancer Screening; POBASCAM, Population Based Screening Study Amsterdam; PPV, positive predictive value; RCT, randomized controlled trial; SwedeScreen, Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Cancer Screening; yr, year or years.

Fig. 4.4 Randomized controlled trials comparing HPV-based screening versus cytology screening: relative risk of CIN2+ and CIN3+ in the first and second screening rounds
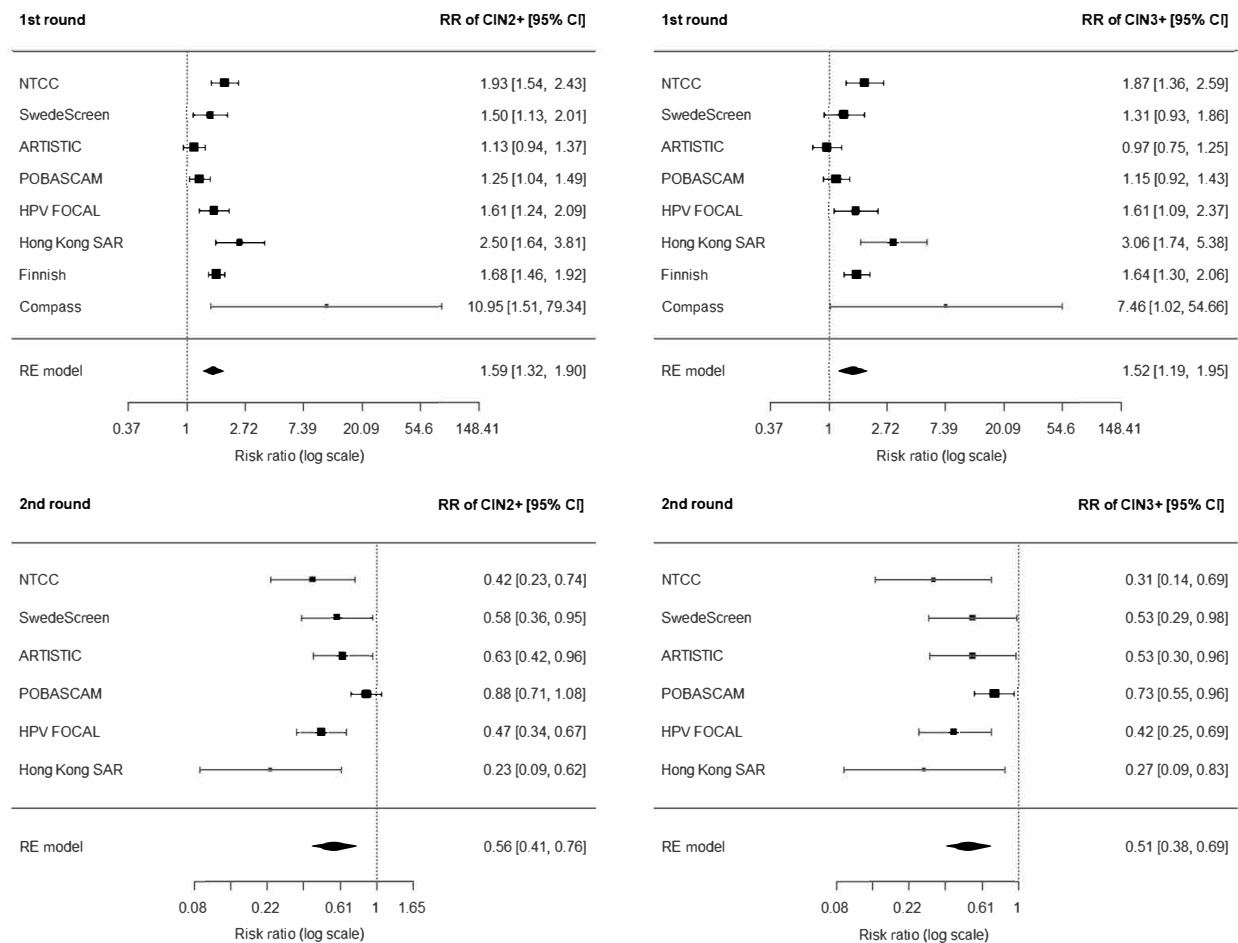
Risk ratio (RR) of CIN2+ (left panel) or CIN3+ (right panel) at first (top) and second (bottom) cervical screening rounds comparing HPV testing with cytology in eight clinical trials.

ARTISTIC, A Randomised Trial In Screening To Improve Cytology; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; HPV FOCAL, HPV For Cervical Cancer Screening; NTCC, New Technologies for Cervical Cancer Screening; POBASCAM, Population Based Screening Study Amsterdam; RE model, random-effects model; SAR, Special Administrative Region; SwedeScreen, Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Cancer Screening.

The pooled estimates were computed by the Working Group based on the data presented in Table 4.22, using the restricted maximum-likelihood estimator method of the metafor library in R for random/mixed-effects models. Source: see Table 4.22 for references.

0.23 (95% CI, 0.09–0.62) in the Hong Kong SAR trial (Chan et al., 2020) to 0.88 (95% CI, 0.71–1.08) in the POBASCAM trial (Rijkaart et al., 2012a), and the relative risk of CIN3+ ranged from 0.27 (95% CI, 0.09–0.83) in the Hong Kong SAR trial (Chan et al., 2020) to 0.73 (95% CI, 0.55–0.96) in the POBASCAM trial (Rijkaart et al., 2012a).

The ARTISTIC, POBASCAM, and Swede-Screen trials also reported the cumulative number of CIN2+ and CIN3+ cases detected in the first and second rounds and during extended follow-up beyond the second round, stratified by the HPV DNA testing and/or cytology result at baseline (Kitchener et al., 2011; Elfström et al., 2014; Dijkstra et al., 2016). In the ARTISTIC trial, the cumulative CIN3+ risk in women with a negative HPV test was 0.13% after two rounds of screening (with an interval of 3 years) and 0.28% after three rounds of screening, whereas the cumulative CIN3+ risk in women with normal cytology was 0.31% after two rounds and 0.63% after three rounds. In the POBASCAM and SwedeScreen trials, separate CIN3+ risks were calculated for the intervention arm and the control arm. In the POBASCAM trial, the cumulative CIN3+ risk in women from the intervention arm with a negative HPV test was 0.31% (95% CI, 0.24–0.41%) after two rounds of screening (with an interval of 5 years) and 0.56% (95% CI, 0.45–0.70%) after three rounds of screening, whereas the cumulative CIN3+ risk in women from the control group with normal cytology was 0.69% (95% CI, 0.58–0.82%) after two rounds and 1.20% (95% CI, 1.01–1.37%) after three rounds (Dijkstra et al., 2016). In the SwedeScreen trial, follow-up data were collected up to 13 years after enrolment and reported for specific time points. The cumulative CIN3+ risk in women from the intervention group with a negative HPV test was 0.04% after 3 years, 0.15% after 5 years, and 0.44% after 10 years, whereas the cumulative CIN3+ risk in women from the control group with normal cytology was 0.20% after 3 years, 0.51% after 5 years, and 0.97%

after 10 years (Elfström et al., 2014). The relative cumulative risk of CIN3+ in HPV-negative women compared with women with normal cytology ranged from 0.42 to 0.57 across trials and time points.

[The studies showed considerable variation in HPV and cytology testing technology, age ranges, and management in the HPV DNA testing intervention arms. Five of the eight RCTs evaluated co-testing with HPV testing and cytology compared with cytology alone. The trials also differed in their methods of disease ascertainment at exit testing. For example, in the NTCC and SwedeScreen trials the second round of screening was conducted with cytology, whereas in the POBASCAM and HPV FOCAL trials the second round of screening was conducted with co-testing with HPV testing and cytology, and in the ARTISTIC trial the screening protocols were the same in the first and second rounds. Furthermore, the definition of the second screening round varied across studies. In some trials (e.g. the POBASCAM and HPV FOCAL trials), the start of the second round was based only on time since enrolment, whereas some other trials also used criteria for the start of the second round that depended on the screening results in the first round. Despite design differences, most trials showed an increase in CIN3+ in the first round, and all trials with two screening rounds showed a decrease in CIN3+ in the second round.]

(iii) *Efficacy of screening for prevention of cervical cancer and associated death*

In the Osmanabad District trial (Sankaranarayanan et al., 2009), different screening strategies (HPV testing, conventional cytology, and VIA) were compared with standard care, but risk ratios for the comparison of HPV testing with cytology can be calculated from the tabulated number of cases and the person-years at risk. The risk ratios for the detection of advanced cancer (International Federation of Gynecology

and Obstetrics [FIGO] stage II or higher) and for cervical cancer mortality in the HPV testing group compared with the cytology group were 0.63 (95% CI, 0.41–0.96) and 0.59 (95% CI, 0.37–0.92), respectively. No reduction in all-cause mortality was observed for any screening intervention group compared with the standard-care control group.

[It is important to bear two issues in mind when interpreting the findings. First, the trial represented the findings of one round of screening in a previously unscreened population. Therefore, risk ratios for cervical cancer mortality are different from those in situations where women are repeatedly screened during their lifetime. Second, although active steps were taken to ascertain vital status and cause of death in the population, it is possible that in this setting there were some limitations in the processes of cancer registration and death ascertainment.]

A pooled analysis of four RCTs conducted in Europe compared the efficacies of HPV DNA testing and cervical cytology for the prevention of invasive cervical cancer (Ronco et al., 2014). This analysis was critical, because it examined an invasive cervical cancer end-point for the first time in a high-income country setting. The pooled analysis included 176 464 women aged 20–64 years who were randomly assigned to HPV-based screening (intervention arm) or cytology-based screening (control arm) in Italy (NTCC), the Netherlands (POBASCAM), Sweden (SwedeScreen), and the United Kingdom (ARTISTIC). Women were followed up for a median of 6.5 years, and during that time 107 invasive cervical carcinomas were detected. Cumulative detection of invasive cervical cancer was lower in the HPV testing arm than in the cytology arm during the study period (rate ratio, 0.60; 95% CI, 0.40–0.89), and no heterogeneity was detected between studies ($P = 0.52$). Detection of invasive cervical carcinoma was similar between screening methods during the first 2.5 years of follow-up (rate ratio, 0.79; 95%

CI, 0.46–1.36) but was significantly lower in the HPV arm thereafter (rate ratio, 0.45; 95% CI, 0.25–0.81). In women with a negative screening test at entry (HPV-negative in the intervention arm and cytology-negative in the control arm), the rate ratio was 0.30 (95% CI, 0.15–0.60). The cumulative incidence of invasive cervical carcinoma in women with negative entry tests was 4.6 (95% CI, 1.1–12.1) per 100 000 women at 3.5 years and 8.7 (95% CI, 3.3–18.6) per 100 000 women at 5.5 years in the HPV testing arm and 15.4 (95% CI, 7.9–27.0) per 100 000 women at 3.5 years and 36.0 (95% CI, 23.2–53.5) per 100 000 women at 5.5 years in the cytology arm. The pooled rate ratio was lower for adenocarcinoma (0.31; 95% CI, 0.14–0.94) than for SCC (0.78; 95% CI, 0.49–1.25). The lowest rate ratios were observed in women aged 30–34 years (0.36; 95% CI, 0.14–0.94).

[The authors found no heterogeneity in efficacy between studies, which supports the pooling of data and the overall pooled findings. It should be noted that data from these trials are representative of women followed up for at least two rounds of screening, which may be different from long-term, steady-state effects of repeated rounds of screening with a particular screening test and management protocol in a population.]

(iv)   Harms

Harms during the first round of screening were measured by the proportion of women referred for colposcopy after a positive screening test and by the PPV for CIN3+ (the proportion of CIN3+ detected in women referred for colposcopy). The number of colposcopy referrals includes women who were referred at baseline or after repeat testing within the same screening round. The proportion of colposcopy referrals was generally higher for HPV-based screening than for cytology-based screening (Table 4.22). The biggest differences in colposcopy referrals between the study arms were found in the NTCC trial (8.0% vs 2.7%) and the Hong Kong SAR trial (9.3% vs 2.0%), in which HPV-positive

women were not offered triage testing but were immediately referred for colposcopy. The PPV for CIN3+ was similar in the two study arms or higher in the cytology arm in all studies, with the exception of the Compass trial, in which the PPV was higher in the HPV-based testing arm (19.5%) than in the cytology arm (3.7%).

[The number of women with a positive screening test result and the number of colposcopies should be interpreted in relation to the number of CIN3+ detected. If the number of CIN3+ is proportional to the number of colposcopy referrals, then the harms per detected CIN3+ remain unchanged.]

A more complete picture of the harms of screening is obtained from the number of diagnostic procedures when measured over multiple rounds of screening. In the HPV FOCAL trial, the cumulative colposcopy referral rates were similar in the two study arms over two rounds of screening, and in the Hong Kong SAR trial, in which HPV-positive women were immediately referred for colposcopy, the cumulative colposcopy referral rate was higher in the HPV testing arm than in the cytology arm (relative colposcopy referral rate, 2.83; 95% CI, 2.47–3.24). Similar results on cumulative biopsy rates were observed in four RCTs conducted in Europe (Ronco et al., 2014). In the ARTISTIC, POBASCAM, and SwedeScreen trials, the cumulative biopsy rate over two rounds of screening was similar in the two study arms, whereas in the NTCC trial, in which HPV-positive women were immediately referred for colposcopy, the biopsy rate was higher in the HPV testing arm than in the cytology arm (relative biopsy rate, 2.24; 95% CI, 2.09–2.39).

An indication of overtreatment of cervical lesions can be obtained by comparing the cumulative detection of CIN2+ between the HPV testing arm and the cytology arm over two screening rounds. The relative risks of CIN2+ can be computed from the numbers in Table 4.22. The relative risk of CIN2+ over two screening rounds (as computed by the Working Group) was 1.01 (95% CI, 0.83–1.23) in the HPV FOCAL trial, 1.03 (95% CI, 0.87–1.23) in the ARTISTIC trial, 1.08 (95% CI, 0.94–1.24) in the POBASCAM trial, and 1.17 (95% CI, 0.92–1.49) in the SwedeScreen trial, suggesting that replacing cytology-based screening with HPV-based screening will lead to only a small increase in overtreatment. In the NTCC trial and the Hong Kong SAR trial, the estimated relative risks of CIN2+ over two screening rounds were 1.54 (95% CI, 1.25–1.89) and 1.54 (95% CI, 1.09–2.18), respectively, suggesting a moderate increase in overtreatment.

[A difference in the detection of CIN2+ between study arms over two screening rounds needs to be interpreted with care. It may indicate that the magnitude of overtreatment of CIN2+ differs between study arms, but it may also simply point at a difference in lead-time gain that is longer than the interval between two consecutive screens. In the POBASCAM and HPV FOCAL trials, in which women in both study arms received co-testing in the second screening round, so that differences in lead-time gain have become minimal after the second round , there was no marked difference in cumulative detection of CIN2+ between study arms over two screening rounds.]

(d) Population-based cohorts

(i) Description

Studies in Argentina (Arrossi et al., 2019), Denmark (Thomsen et al., 2020), Finland (Veijalainen et al., 2019), Italy (Pasquale et al., 2015; Maggino et al., 2016; Passamonti et al., 2017; Zorzi et al., 2017), the Netherlands (Aitken et al., 2019), Sweden (Lamin et al., 2017), and the United Kingdom (Rebolj et al., 2019) have reported on the impact of primary HPV DNA screening in national, regional, or pilot screening programmes on precancer and cancer. In all cohort studies, HPV DNA-positive women were triaged with cytology to improve the balance between benefits

and harms. There was considerable variation with respect to the follow-up of HPV-positive women with NILM cytology, who were followed up with cytology in the Netherlands, with HPV testing in Argentina, Finland, and Italy, and with combined HPV testing and cytology in Denmark and the United Kingdom, and were re-invited at the next screening round in Sweden. The studies in Argentina, Finland, Italy, and the Netherlands compared primary HPV-based screening programmes with the cytology-based screening programmes that were offered before the implementation of HPV screening. The study in the United Kingdom compared a pilot HPV-based screening implementation cohort with a cytology-based programme running in the same period and region, and the studies in Denmark and Sweden conducted a randomized health services trial with a primary HPV-based screening arm and a cytology-based screening arm.

Co-testing with HPV testing and cytology has been implemented as a screening option in the USA. In 2003, Kaiser Permanente Northern California (KPNC), a large health maintenance organization, adopted screening based on co-testing, with a 3-year interval after a double-negative screening result. The KPNC cohort comprises about 1 million women aged 30–64 years who have received up to four rounds of co-testing (Castle et al., 2019). Co-testing has also been implemented as a pilot programme in the Wolfsburg region in Germany: the Wolfsburg Pilot Project for Better Prevention of Cervical Cancer with Primary HPV Screening (WOLPHSCREEN). By 2016, the WOLPHSCREEN programme had enrolled 26 624 women aged 30–70 years (Horn et al., 2019). The WOLPHSCREEN programme has a 5-year screening interval after a double-negative screening result. In 2019, women had completed up to three screening rounds. Co-testing cohorts do not have a control group, but comparisons between HPV testing and cytology screening

can be made on the basis of the co-testing results. These comparisons are particularly suitable for determining screening intervals (Katki et al., 2011). Further study features of the primary HPV testing and co-testing cohorts, such as study size, age range, and follow-up protocol for HPV DNA-positive women, are given in Table 4.23.

Several other studies have been conducted with one round of co-testing followed by cytology screening in subsequent rounds. These include a pooled analysis of seven studies in European countries (Dillner et al., 2008), including 24 295 women followed up until 6 years after HPV testing who had at least one cervical cytology or histopathology examination during follow-up. Four other studies with a single round of co-testing are available: (i) the HPV in Addition to Routine Testing (HART) study, including 8735 women aged 30–60 years at five clinical centres in the United Kingdom, with a median follow-up of 6 years (Mesher et al., 2010); (ii) the Canadian Cervical Cancer Screening Trial (CCCaST) study, including 4400 women aged 30–69 years in Montreal, with a median follow-up of 1.5 years, and 5754 women aged 30–69 years in St. John's, with a maximum follow-up of 10 years (Isidean et al., 2016); (iii) the Vrije Universiteit Medical Centre-Saltro Laboratory Population-Based Cervical Screening (VUSA-Screen) study, including 25 871 women aged 29–61 years in Utrecht in the Netherlands, with a maximum follow-up of 3 years (Rijkaart et al., 2012b); and (iv) the Addressing the Need for Advanced HPV Diagnostics (ATHENA) study, including 41 955 women aged 25 years and older at 61 clinical centres in the USA, with a follow-up of 3 years (Wright et al., 2015).

(ii) Detection of CIN2+ and CIN3+

The results of the primary HPV screening cohorts with cytology triage for HPV DNA-positive women were consistent with those of the RCTs, because the detection rates of CIN2+ and CIN3+ were always at least as high

Table 4.23 Population-based cohorts: comparison of screening with HPV DNA testing alone or with co-testing versus cytology

Country Reference	Type of study	No. of screened subjects Age (years)	Colposcopy referral recommendation	HPV DNA+/ co-test+ (%)	HPV versus cytology, RR[a] (95% CI)				
					Test-positive	Colposcopy referral	CIN2+	CIN3+	PPV for CIN3+
Argentina Arrossi et al. (2019)	Primary HPV with cytology triage, regional programme (Jujuy)	49 565 30–60	ASC-US, HPV+ at 18 mo	13.6	3.42 (3.22–3.64)	2.69[b] (2.42–2.99)	1.76 (1.52–2.03)	1.90 (1.61–2.24)	1.13 (1.00–1.29)
Denmark Thomsen et al. (2020)	Primary HPV with cytology triage, randomized pilot implementation	11 339 30–59	ASC-US, HPV16/18+, HPV+ or ASC-US at 12 mo	8.8	3.84 (3.42–4.30)	1.81[b] (1.58–2.07)	1.51[b] (1.21–1.89)	1.40[b] (1.07–1.82)	0.77 (0.62–0.97)
Finland Veijalainen et al. (2019)	Primary HPV with cytology triage, regional programme (Tampere)	17 770 35–60	LSIL, HPV+ or LSIL at 12 mo	8.2	1.10 (1.02–1.19)	1.98 (1.75–2.24)	2.45 (1.76–3.41)	2.70 (1.75–4.17)	1.36 (0.90–2.06)
Germany Luyten et al. (2014)	WOLPHSCREEN cohort. Co-testing, regional pilot programme (Wolfsburg)	19 795 30–70	HPV+ and ASC-US, ASC-US at 6 mo, HPV+ at 12 mo	7.5	2.76 (2.51–3.04)	3.22 (2.87–3.60)	2.50 (2.17–2.87)	2.25 (1.90–2.66)	0.70 (0.59–0.83)
Italy Pasquale et al. (2015)	Primary HPV with cytology triage, regional programme (Valcamonica)	18 728 25–64	ASC-US, HPV+ at 12 mo	8.7	2.33 (2.14–2.54)	1.71 (1.56–1.88)	1.59 (1.23–2.07)	NR	NR
Italy Maggino et al. (2016)	Primary HPV with cytology triage, regional programme (Venice)	89 217 25–64	ASC-US, HPV+ at 12 mo	6.8	2.35 (2.25–2.46)	1.78 (1.70–1.87)	2.23 (1.87–2.65)	NR	NR
Italy Passamonti et al. (2017)	Primary HPV with cytology triage, regional programme (Perugia)	6272 25–64	ASC-US, HPV+ at 12 mo	6.3	4.19 (3.57–4.92)	4.00 (3.29–4.87)	2.65 (1.85–3.78)	NR	NR

Table 4.23 (continued)

Country Reference	Type of study	No. of screened subjects Age (years)	Colposcopy referral recommendation	HPV DNA+/ co-test+ (%)	HPV versus cytology, RR[a] (95% CI)				
					Test-positive	Colposcopy referral	CIN2+	CIN3+	PPV for CIN3+
Italy Zorzi et al. (2017)	Primary HPV with cytology triage, regional programme (Padua)	48 763 25–64	ASC-US, HPV+ at 12 mo	6.4	NR	NR	1.2 (0.9–1.7)	NR	NR
Netherlands Aitken et al. (2019)	Primary HPV with cytology triage, national programme	454 573 29–61	ASC-US, ASC-US at 6 mo	9.1[c]	1.89 (1.86–1.92)	1.97 (1.92–2.02)	1.34 (1.29–1.39)	1.28 (1.23–1.35)	0.65 (0.63–0.68)
Sweden Lamin et al. (2017)	Primary HPV with cytology triage, randomized pilot implementation (Stockholm)	7325 56–60	ASC-US	5.5	2.69 (2.24–3.23)	1.18 (0.81–1.71)	1.07 (0.56–2.04)	1.02 (0.47–2.19)	0.86 (0.44–1.69)
United Kingdom Rebolj et al. (2019)	Primary HPV with cytology triage, non-randomized pilot implementation	183 970 24–64	ASC-US, HPV+ and ASC-US at 12 mo, HPV+ at 24 mo	12.7	3.31 (3.25–3.38)	1.85 (1.80–1.89)	1.46 (1.40–1.52)	1.41 (1.34–1.48)	0.76 (0.73–0.80)
USA Castle et al. (2019)	KPNC cohort. Co-testing, regional cohort (Northern California)	990 013 30–64	LSIL, HPV+ and ASC-US, HPV+ or ASC-US at 12 mo	8.0	1.30 (1.29–1.32)	NR	NR	1.36 (1.33–1.39)	NR

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; HPV, human papillomavirus; KPNC, Kaiser Permanente Northern California; LSIL, low-grade squamous cell intraepithelial lesion; mo, month or months; NR, not reported; PPV, positive predictive value; RR, relative risk; WOLPHSCREEN, Wolfsburg Pilot Project for Better Prevention of Cervical Cancer with Primary HPV Screening.

[a] The relative risks, computed by the Working Group, are based on absolute numbers reported in the original publications. The 95% confidence intervals were calculated using a normal reference distribution for the logarithm of the estimated relative risk.

[b] Baseline only; no repeat testing information used.

[c] Absolute numbers were not available; based on proportions reported in the article.

with HPV screening as with cytology screening (Table 4.23). In studies that reported on both CIN2+ and CIN3+ cases, the relative risks of HPV testing versus cytology were similar for both end-points. The relative risks for the detection of CIN2+ varied from 1.07 (95% CI, 0.56–2.04) in the study in Sweden (restricted to women aged 56–60 years) to 2.65 (95% CI, 1.85–3.78) in the study in Perugia in Italy.

[In the studies in Argentina and Denmark, follow-up data for HPV-positive women with NILM cytology were incomplete. This may have led to an underestimation of the relative detection risk, because women with NILM cytology have a relatively low CIN2+ risk.]

Most countries implemented primary HPV screening with cytology triage in women older than 30 years, but in some regions in Italy and in the United Kingdom, HPV screening was also studied in women aged from 24 or 25 years to 29 years. In the areas of Padua, Valcamonica, and Venice in Italy, the risks of CIN2+ per screened woman were 1.0%, 2.1%, and 1.1%, respectively, in women younger than 30 years and 0.4%, 0.6%, and 0.4%, respectively, in women aged 30 years and older (Pasquale et al., 2015; Maggino et al., 2016; Zorzi et al., 2017). In the pilot implementation cohort in the United Kingdom, the risk of CIN2+ per screened woman was 6.6% in women younger than 30 years and 1.2% in women aged 30 years and older, and the risk of CIN3+ per screened woman was 4.0% in women younger than 30 years and 0.8% in women aged 30 years and older (Rebolj et al., 2019).

This risks of CIN2+ and CIN3+ in subsequent screening rounds were also studied in the cohorts in Italy. In the cohort in Padua (Zorzi et al., 2017), the CIN2+ risk in the second round after 3 years was 0.11% per screened woman and the CIN3+ risk was 0.03%. The relative risk of CIN2+ in the second round versus the first round was 0.24 (95% CI, 0.16–0.37), and the relative risk of CIN3+ was 0.14 (95% CI, 0.06–0.32). In the cohort in Perugia (Passamonti et al., 2017), the

risks of CIN2+ and CIN3+ in the second round after 3 years were 0.25% and 0.17%, respectively, and the relative risks of CIN2+ and CIN3+ were 0.25 (95% CI, 0.14–0.42) and 0.39 (95% CI, 0.20–0.79), respectively. In a study of three cohorts in Italy (Del Mistro et al., 2019), the relative risks of CIN2+ and CIN3+ in the second round versus the first round were found to be higher when an HPV infection was reported in the previous round, and also when the positive HPV test result was followed by a negative HPV test result during short-term repeat testing. This finding was also reported for the intervention arm of the POBASCAM trial (Polman et al., 2017).

[The low risks of CIN2+ and CIN3+ in the second primary HPV screening round support the use of intervals of longer than 3 years when the primary HPV test result in the previous round is negative.]

Table 4.23 also shows the results of the cohorts in which co-testing with HPV testing and cytology has been implemented: the WOLPHSCREEN cohort in Germany and the KPNC cohort in the USA. For both studies, substantially higher CIN3+ risks were observed after a positive HPV test result than after abnormal cytology. In addition, in the KPNC cohort, the 5-year CIN3+ risk was 0.11% after a negative HPV test result and 0.25% after an NILM cytology result (Castle et al., 2018). In the WOLPHSCREEN cohort, the 5-year CIN3+ risk was 0.013% after a negative HPV test result and 0.071% after an NILM cytology result (Horn et al., 2019). Cohorts with only one round of co-testing followed by cytology follow-up yielded results that were in line with those from the KPNC and WOLPHSCREEN cohorts. In a pooled study of seven European cohorts (Dillner et al., 2008), the pooled 5-year CIN3+ risk was 0.27% after a negative HPV test result and 0.83% after an NILM cytology result. The VUSA-Screen study reported a 3-year CIN3+ risk of 0.06% after a negative HPV test result and 0.26% after NILM

cytology, and the ATHENA study reported a 3-year CIN3+ risk of 0.3% after a negative HPV test result and 0.8% after NILM cytology. The HART study and the CCCaST study reported risks only for the end-point CIN2+. In the HART study, the 3-year CIN2+ risk was 0.04% after a negative HPV test result and 0.21% after NILM cytology, and the 5-year CIN2+ risk was 0.15% after a negative HPV test result and 0.28% after NILM cytology. In the CCCaST study, the 3-year CIN2+ risk was 0.90% after a negative HPV test result and 1.40% after NILM cytology.

(iii) Detection of cervical cancer

The two largest primary HPV screening cohorts, in the United Kingdom (Rebolj et al., 2019) and the Netherlands (Aitken et al., 2019), reported on cervical cancer detection over one round of screening and compared it with the cancer detection in a historical cytology screening cohort. In the cohort in the United Kingdom, cervical cancer detection over one round of screening was 0.05% for HPV DNA screening and 0.04% for cytology screening, and the adjusted odds ratio for cervical cancer detection was 1.27 (95% CI, 0.99–1.63) (Rebolj et al., 2019). In the cohort in the Netherlands, cervical cancer detection over one round was 0.04% for HPV DNA screening and 0.03% for cytology screening (Aitken et al., 2019).

In the KPNC co-testing cohort, the 5-year cancer risk was 0.5% after a positive HPV DNA test result and 0.5% after abnormal cytology (Castle et al., 2019). In the subgroup of women with a negative HPV test result (Castle et al., 2018), the 5-year cancer risk was 0.009%, which was about 40% lower than the 5-year cancer risk of 0.02% after an NILM cytology result. The cancer risk after a negative HPV test result further decreased after previous rounds of negative HPV testing: the 5-year cancer risk was 0.004% after two rounds of negative HPV DNA testing and 0.002% after three rounds of negative HPV DNA testing. The results from the KPNC cohort were supported by the findings of the WOLPHSCREEN study, in which the risk of cancer in the first co-testing screening round was 0.10%, which further decreased to 0.03% in subsequent rounds (Horn et al., 2019).

[Together, the RCTs, the primary HPV screening cohorts, and the co-testing cohorts demonstrate that a negative HPV test result gives better reassurance against CIN3+ and cancer than does NILM cytology, and supports the use of longer screening intervals.]

(iv) Harms

In the primary HPV screening cohorts, both the proportion of screen-positive women and the proportion of colposcopy referrals were higher than in cytology screening cohorts (Table 4.23). However, the proportions varied widely across studies. The relative proportion of screen-positive women varied from 1.10 (95% CI, 1.02–1.19) in the study in Finland to 3.84 (95% CI, 3.42–4.30) in the study in Denmark, and the relative proportion of colposcopy referrals varied from 1.18 (95% CI, 0.81–1.71) in the study in Sweden to 4.00 (95% CI, 3.29–4.87) in the study in Perugia in Italy. The proportion of CIN3+ per colposcopy referral (PPV for CIN3+) was below 1 in most settings (up to 35% lower in the Netherlands) but was higher in the studies in Argentina (RR, 1.13; 95% CI, 1.00–1.29) and in Finland (RR, 1.36; 95% CI, 0.90–2.06). In Italy, the studies in Perugia (Passamonti et al., 2017) and in Padua (Zorzi et al., 2017) also reported on the colposcopy referrals in the second HPV-based screening round. The proportion of colposcopy referrals per screened woman in the second round decreased by 10% (95% CI, −6% to 25%) in the Perugia cohort and by 51% (95% CI, 46–55%) in the Padua cohort compared with the first HPV-based screening round. The proportion of CIN3+ per colposcopy referral decreased by 58% (95% CI, 17–78%) in the Perugia cohort and by 71% (95% CI, 35–87%) in the Padua cohort.

[It must be recognized that the follow-up of HPV-positive women with NILM cytology was incomplete in the studies in Argentina and Denmark, and that in Sweden, HPV-positive women with NILM cytology did not receive short-term follow-up testing. This may influence the proportion of colposcopy referrals, which was lowest in Sweden. The high PPV for CIN3+ in the study in Finland is a direct consequence of the high relative detection rate of CIN3+ per screened woman in this study, which was the highest among the studies that reported on CIN3+ cases.]

Consistent with results from the primary HPV screening cohorts, the proportion of screen-positive women was higher for HPV testing than for cytology in the two co-testing cohorts (KPNC and WOLPHSCREEN). The WOLPHSCREEN cohort also reported that the number of colposcopy referrals in HPV-positive women was 3.22 (95% CI, 2.87–3.60) times that in women with abnormal cytology; the corresponding relative PPV for CIN3+ after colposcopy referral was 0.70 (95% CI, 0.59–0.83).

[Both triage testing of HPV-positive women and suitable follow-up management of HPV-positive women with NILM cytology results are important to achieve a good balance between screening benefits and harms. Nonetheless, the results from population-based cohorts indicated that an increase in the number of colposcopy referrals can be expected in the first round of HPV-based screening.]

4.4.3 Comparison of HPV DNA testing versus VIA

(a) Introduction

No review was available that directly compared the impact of HPV DNA testing and VIA on cervical cancer incidence, mortality, and detection.

Evidence about diagnostic accuracy was extracted from eight reviews and meta-analyses or pooled analyses across a wide range of geographical regions. Data were drawn from observational studies, and mostly cross-sectional studies; this may limit the strength of the evidence. In addition, the original studies included in the reviews and analyses had not necessarily compared HPV DNA testing and VIA directly. Thus, the pooled results may potentially be affected by multiple factors, including but not limited to (i) non-comparability of control groups, (ii) different screening participation rates across studies, and (iii) heterogeneity in quality assurance and monitoring methods. Moreover, the performance of VIA, which is a technique that is highly subjective and heavily dependent on the training and experience of providers, varied widely across different populations and research settings (see Sections 4.2.1–4.2.3). In addition, in many studies in which VIA was evaluated, colposcopy plus directed biopsy used as the reference were generally applied to women with a positive screening test result only, potentially leading to verification bias. Furthermore, colposcopy could miss up to 40% of prevalent precancers and is closely correlated with visual screening approaches (see Section 4.2.2); such potential outcome misclassification with VIA may greatly affect the estimates of the test accuracy. Given the above-mentioned limitations, in comparisons of HPV DNA testing with VIA, the results for accuracy parameters must be interpreted with caution.

The detection rate of cervical neoplasia and cancer was assessed mainly by two RCTs, a pooled analysis of two cohort studies, and three cross-sectional studies, one of which was applied in a real-world setting in China.

The incidence of and mortality from cervical cancer were assessed by an RCT in Osmanabad District in India, which was the only study available.

Table 4.24 Accuracy of HPV DNA testing versus visual inspection with acetic acid (VIA)

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI) Relative specificity (95% CI)	Comments
			HPV	VIA	HPV	VIA		
Arbyn et al. (2008) Pooled analysis of > 58 000 women aged 25–64 yr recruited from 11 cross-sectional studies in urban settings in India and French-speaking countries in Africa in 1999–2003	HPV DNA test, VIA, VILI, VIAM, cytology (see comments) 25–64 CIN2+, CIN3+, cancer	VIA: 16.7; range, 6.0–27.4	CIN2+: 61.9 (56.2–67.7); range, 48.4–67.7 CIN3+: 68.4 (61.5–75.4); range, 62.3–73.5 Cancer: 72.1 (60.3–83.8); range, 61.5–85.7	CIN2+: 79.2 (73.3–85.0); range, 65.0–91.1 CIN3+: 82.9 (77.1–88.7); range, 58.3–94.6 Cancer: 88.7 (83.1–94.3); range, 66.7–100.0	CIN2+: 93.6 (92.4–94.8); range, 91.6–94.6 CIN3+: 93.4 (92.2–94.6); range, 91.4–94.4 Cancer: 93.0 (91.8–94.2); range, 91.4–94.0	CIN2+: 84.7 (80.7–88.0); range, 74.2–94.5 CIN3+: 84.2 (80.0–88.3); range, 73.8–94.3 Cancer: 83.6 (79.3–88.0); range, 73.1–94.1	HPV vs VIA: CIN2+: 0.883 (0.775–1.007) CIN3+: 0.956 (0.781–1.169) HPV vs VIA: CIN2+: 1.074 (1.051–1.097) CIN3+: 1.075 (1.051–1.099)	Evidence from observational studies. Not every study included had assessed the HPV DNA test and VIA concurrently. HPV DNA test (HC2) was applied in 4 studies in India, and VIA was used in all 11 studies in both Africa and India
Zhao et al. (2010) Pooled analysis of individual patient data in 28 848 women from 17 population-based, cross-sectional cervical cancer screening studies in both urban and rural areas in 9 provinces in China in 1999–2008. The eligible women were sexually active, were not pregnant, had an intact uterus, and had no history of CIN or cervical cancer	HPV DNA test, VIA, cytology 17–59 CIN2+, CIN3+	HPV: 16.3 (4691 of 28 848 women) VIA: 10.8 (3122 of 28 815 women)	Uncorrected: CIN2+: 96.3 (94.9–97.4) CIN3+: 97.5 (95.7–98.7) Corrected: CIN2+: 95.1 (93.6–96.3) CIN3+: 97.6 (95.9–98.6)	CIN2+: 48.0 (42.1–53.9); range, 12.5–70.2 CIN3+: 54.6 (48.0–61.2); range, 14.3–85.7	Uncorrected: CIN2+: 86.4 (83.8–89.0) CIN3+: 85.1 (82.3–87.9) Corrected: CIN2+: 85.4 (85.0–85.8) CIN3+: 84.1 (83.7–84.5)	CIN2+: 90.4 (87.3–93.5); range, 70.0–98.2 CIN3+: 89.9 (86.8–93.0); range, 69.9–97.5	NR NR	Evidence from observational studies. Women included in the pooled analysis all concurrently received HPV DNA test, LBC, and VIA

Table 4.24 (continued)

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI) Relative specificity (95% CI)	Comments
			HPV	VIA	HPV	VIA		
Chen et al. (2012) 101 299 apparently healthy women from 22 cross-sectional studies (99 972 women tested by VIA, 23 628 women tested by HPV DNA test). 6 common cervical screening strategies including VIA and HPV DNA test were assessed	HPV DNA test, VIA, VIAM, VILI, cytology (see comments) 16–70 CIN2+	NR	74 (69–78)	77 (75–78)	92 (92–93)	87 (87–88)	NR NR	Studies included in the review underwent quality assessment with QUADAS and STARD quality assessment criteria. Evidence from observational studies. Not every study included had assessed the HPV DNA test and VIA concurrently. Three types of HPV DNA test were involved (HC2, PCR, and *care*HPV), but only the HC2 assay with samples collected by health professionals was used to estimate the accuracy of HPV testing in this meta-analysis

Table 4.24 (continued)

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI) Relative specificity (95% CI)	Comments
			HPV	VIA	HPV	VIA		
Fokom-Domgue et al. (2015) 8 studies in which the reference standard (colposcopy and colposcopy-directed biopsy) was performed in all women of the study population from sub-Saharan Africa were included. The study population was not at particular risk of cervical cancer (studies focusing on HIV-positive women or on women presenting with gynaecological symptoms were excluded). In total, 47 361 women were screened with VIA and 3950 women were screened with HPV DNA test	HPV DNA test, VIA, VILI 15–83 CIN2+	HPV: 25.8 (17.4–35.3); range, 12.5–42.8 VIA: 16.8 (11.0–23.6); range, 3.1–39.9	88.3 (73.1–95.5); range, 80.2–96.2	82.4 (76.3–87.3); range, 65.0–94.4	73.9 (50.7–88.7); range, 61.2–88.9	87.4 (77.1–93.4); range, 64.1–98.2	VIA vs HPV: 0.94 (0.82–1.16) VIA vs HPV: 1.17 (0.95–1.69)	Studies included were assessed as of moderate quality, based on the QUADAS-2 criteria. Evidence from observational studies. Not every study included had assessed the HPV DNA test and VIA concurrently. Test accuracy was assessed only among the studies in which the reference test (colposcopy and colposcopy-directed biopsy) was performed in all women (10 studies for VIA, 3 studies for HPV), which may avoid verification bias

Table 4.24 (continued)

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI) Relative specificity (95% CI)	Comments
			HPV	VIA	HPV	VIA		
Bobdey et al. (2015) 16 studies conducted in India in 1990–2013 were included. Pooled data of 89 461 women in the VIA arm from 14 studies and 23 244 women in the HPV test arm from 8 studies were analysed	HPV DNA test, VIA, VIAM, VILI, cytology NA NR	NR	75.04; range, 45.70–97.10	68.76; range, 31.60–100.00	91.66; range, 84.20–94.60	84.02; range, 53.30–91.23	NR NR	No quality assessment criteria were applied in the 2 reviews. The age range of included participants and disease end-points of assessment, and the 95% CI of the pooled results on accuracy were not reported. Evidence from observational studies. Not every study included had assessed the HPV DNA test and VIA concurrently. Some included studies were conducted in the health clinics including gynaecologically symptomatic women. Thus, the pooled results of accuracy in the reviews consisted of both asymptomatic and symptomatic participants, which may limit the generalizability to healthy women
Bobdey et al. (2016) 11 studies conducted in India in 1990–2015 were included. Pooled number of women in the VIA arm was 57 225 and in the HPV DNA test arm was 25 575	HPV DNA test, VIA, VIAM, VILI, cytology NA NR	NR	77.81	67.65	91.54	84.32	NR NR	

Table 4.24 (continued)

Reference Study population	Screening exposure Age of included subjects (years) End-point	Test positivity rates (%) (95% CI)	Sensitivity estimate, % (95% CI)		Specificity estimate, % (95% CI)		Relative sensitivity (95% CI) Relative specificity (95% CI)	Comments
			HPV	**VIA**	**HPV**	**VIA**		
[Mustafa et al. (2016)](#) 5 cross-sectional studies with a total of 8921 non-pregnant women not previously diagnosed with cervical neoplasia were included	HPV DNA test, VIA, cytology ≥ 18 CIN2/3	HPV: 17.6 VIA: 14.1	95 (84–98); range, 64–97	69 (54–81); range, 41–87	84 (72–91); range, 56–93	87 (79–92); range, 76–95	NR NR	All the included studies underwent quality assessment with QUADAS criteria. Evidence from observational studies. Women included in the studies had all concurrently received HPV DNA test and VIA
[Holt et al. (2017)](#) Data of 2757 postmenopausal women were extracted from the 17 population-based studies in [Zhao et al. (2010)](#) for further analysis	HPV DNA test, VIA, cytology 17–59 CIN2+, CIN3+	HPV: 17.2 (15.9–18.7) VIA: 6.2 (5.3–7.1)	CIN2+: 82/84, 97.6 (92.4–99.6) CIN3+: 47/48, 97.9 (90.2–99.9)	CIN2+: 26/84, 31.0 (21.8–41.4) CIN3+: 20/48, 41.7 (28.4–55.9)	CIN2+: 2280/2673, 85.3 (83.9–86.6) CIN3+: 2281/2709, 84.2 (82.8–85.5)	CIN2+: 2529/2673, 94.6 (93.7–95.4) CIN3+: 2559/2709, 94.5 (93.6–95.3)	NR NR	This is a further stratification analysis after the pooled analysis of 17 cross-sectional studies described in [Zhao et al. (2010)](#)

CI, confidence interval, CIN, cervical intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HC2, Hybrid Capture 2; HPV, human papillomavirus; LBC, liquid-based cytology; mo, month or months; NR, not reported; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; STARD, Standards for Reporting of Diagnostic Accuracy Studies; VIA, visual inspection with acetic acid; VIAM, visual inspection with acetic acid using low-level magnification; VILI, visual inspection with Lugol's iodine.

(b)   Accuracy of HPV DNA testing versus VIA

Studies comparing the accuracy of HPV DNA testing versus VIA are presented in Table 4.24. Most of the reviews reported a higher pooled sensitivity for HPV DNA testing compared with VIA, and the clinical performance of VIA varied greatly across different geographical areas and studies, which highlighted the difficulties in achieving reliable performance of VIA (Arbyn et al., 2008; Zhao et al., 2010; Chen et al., 2012; Bobdey et al., 2015, 2016; Fokom-Domgue et al., 2015; Mustafa et al., 2016). The sensitivity of HPV DNA testing for detection of CIN2+ varied from 61.9% with HC2 test data pooled from studies in India (Arbyn et al., 2008) to 96.3% in the pooled analysis in China (Zhao et al., 2010); the sensitivity of VIA for detection of CIN2+ varied from 48.0% in the pooled analysis in China (Zhao et al., 2010) to 82.4% in the meta-analysis in sub-Saharan Africa (Fokom-Domgue et al., 2015), and VIA positivity rates were variable across studies. The specificity of HPV DNA testing for CIN2+ ranged between 84% and 93.6% in all reviews and analyses, except in the meta-analysis in sub-Saharan Africa (73.9%) (Fokom-Domgue et al., 2015); the specificity of VIA for CIN2+ varied from 84% in India (Bobdey et al., 2015) to 90.4% in China (Zhao et al., 2010).

In the pooled analysis of Zhao et al. (2010), a large proportion of participants had received directed biopsies and random biopsies under colposcopy, whereas in the meta-analysis of Fokom-Domgue et al. (2015), colposcopy and directed biopsies performed in all women occurred in only a few of the studies analysed. [Careful consideration is needed when interpreting the accuracy of VIA across different study settings.]

HPV DNA testing has been shown to be superior to VIA as a primary screening technique in detecting cervical neoplasia in postmenopausal women. The study of Holt et al. (2017) found that the sensitivity of HPV DNA testing for both CIN2+ and CIN3+ remained stable near 98%, whereas the corresponding sensitivity of VIA decreased significantly, to 31.0% for CIN2+ and 41.7% for CIN3+.

However, in the study of Arbyn et al. (2008), the pooled sensitivity of HPV DNA testing for CIN2+ was substantially lower than that of VIA (61.9% vs 79.2%), although this difference was not statistically significant (relative sensitivity of HPV vs VIA, 0.883; 95% CI, 0.775–1.007). Several potential explanations for the relatively low sensitivity of HC2 testing have been discussed, including sample contamination or deterioration, limited scope of the hrHPV DNA probe, and misclassification of the outcome, which may result in overestimation of the sensitivity of VIA and underestimation of the sensitivity of HPV DNA testing. Arbyn et al. (2008) reported a relatively high correlation (0.61) between results of VIA and the reference standard (colposcopy), compared with the low correlation (0.13) between results of HC2 testing and colposcopy. [The Working Group noted that VIA and colposcopy were often performed at the same time by health workers who had been trained just before the study began. Potential bias may occur in favour of a test when the test is verified with an imperfect reference standard and results of the two techniques are correlated (e.g. similar inspection after application of acetic acid for both VIA and colposcopy).]

[There is also a potential issue concerning the correlation of reported pooled results, given the overlap between studies being included in different reviews. For example, the study of Sankaranarayanan et al. (2004) has been included in five reviews (Arbyn et al., 2008; Chen et al., 2012; Bobdey et al., 2015, 2016; Fokom-Domgue et al., 2015).] This study was conducted in India and included 18 085 apparently healthy, asymptomatic women aged 25–65 years who were screened with HPV DNA testing, cytology, VIA, and VILI concurrently. The study reported a relatively low sensitivity for both HPV testing

and VIA at some study sites (e.g. in Kolkata, the sensitivity of HPV testing for CIN2/3 was 45.7%, and the sensitivity of VIA was 54.4%). Potential reasons were discussed by the authors, such as the variable expertise of screening providers in specimen collection, unsatisfactory specimens, or DNA losses during HC2 testing (Sankaranarayanan et al., 2004). [The Working Group noted that when studies with such large sample sizes are included, the potential impact on the pooled results in the reviews must be considered.]

(c)   Detection rate of cervical neoplasia and cancer with HPV DNA testing versus VIA

Two cluster RCTs in India and South Africa, three cross-sectional studies in China and India, and a pooled analysis of two cohort studies in eastern Europe and Latin America have compared the detection rates of cervical precancer and cancer according to HPV DNA testing and VIA results (Denny et al., 2005, 2010; Sankaranarayanan et al., 2005, 2009; Sarian et al., 2010; Asthana & Labani, 2015; Basu et al., 2015; Zhao et al., 2018). These studies are presented in Table 4.25 and below.

Overall, HPV DNA testing yielded higher detection rates of high-grade cervical lesions compared with VIA.

The RCT conducted in Osmanabad District in India involved 131 746 women aged 30–59 years from October 1999 to November 2003. Clusters, consisting of villages, were randomized into four groups: HPV DNA testing (HC2), VIA, cytology, and a control group that received only health education but no screening at baseline. Immediate colposcopy was offered and directed biopsies were taken from abnormal areas for women in the VIA group. In the other screening groups, colposcopy appointments were made for women who tested positive, and punch biopsy specimens were taken if abnormal findings were present. The HPV testing, VIA, and cytology groups had positivity rates of 10.3%, 13.9%, and 7.0%, respectively, and colposcopy compliance rates of 89.1%, 98.7%, and 87.9%, respectively (Sankaranarayanan et al., 2005, 2009). According to the colposcopy and biopsy findings at baseline, the detection rates were 0.9% for CIN2/3 and 0.3% for cervical cancer in the HPV arm; the detection rates in the VIA arm were similar, at 0.7% for CIN2/3 and 0.3% for cervical cancer.

The other RCT was conducted in South Africa from June 2000 to December 2002. A total of 6555 women aged 35–65 years were recruited, and HPV DNA testing (HC2) was compared with VIA in a screen-and-treat strategy (Denny et al., 2005, 2010). All the participants were screened with HPV DNA testing and VIA at baseline and subsequently randomized to either HPV-and-treat or VIA-and-treat, or to a control group with evaluation delayed for 6 months. Women with a positive test result in both the HPV-and-treat and VIA-and-treat groups underwent cryotherapy. In the HPV DNA testing group, 467 of 2163 women (22%) underwent cryotherapy; in the VIA group, 482 of 2227 women (22%) underwent cryotherapy. At 6 months after randomization, colposcopy was performed by a physician blinded to the group assignment and clinical information for all women. Biopsies were taken for all acetowhite lesions, and appropriate treatment was given for women with CIN2+. At 6 months, the prevalence of CIN2+ was 0.80% (95% CI, 0.40–1.20%) in the HPV-and-treat group, 2.23% (95% CI, 1.57–2.89%) in the VIA-and-treat group, and 3.55% (95% CI, 2.71–4.39%) in the control group. The efficacy of each screen-and-treat approach was presented as the percentage difference in CIN2+ attributable to the approach [(control group − treatment group)/control group]. At the 6-month evaluation, there was a 77% reduction in prevalent CIN2+ in the HPV-and-treat group and a 37% reduction in the VIA-and-treat group compared with the control group. All women with positive HPV DNA or VIA results at enrolment, plus a subset of women who were both HPV DNA-negative and VIA-negative and were

Table 4.25 Detection rates of cervical neoplasia and cancer with HPV DNA testing versus visual inspection with acetic acid (VIA)

Reference Country	Study description	Detection rates for different disease end-points (%) (95% CI), *n/N*		Comments
		HPV	**VIA**	
Denny et al. (2005, 2010) South Africa	RCT design. 6555 unscreened non-pregnant Black women aged 35–65 yr in Khayelitsha, South Africa, were recruited in 2000–2002. All women were screened using HPV DNA test and VIA at baseline, and subsequently randomized to HPV-and-treat (*n* = 2163), VIA-and-treat (*n* = 2227), or control arm (*n* = 2165) with delayed evaluation. All were recalled for colposcopy and biopsy confirmation at 6 mo. In addition, 2708 of them, who were free of CIN2+ at 6 mo, who were HPV DNA-positive or VIA-positive at baseline, plus a subset of women who were both HPV DNA-negative and VIA-negative, were followed up at 12 mo and 36 mo	CIN2+: At 6 mo: 0.80 (0.40–1.20) At 12 mo: 1.42 (0.87–1.97) At 36 mo: 1.50 (NA)	CIN2+: At 6 mo: 2.23 (1.57–2.89) At 12 mo: 2.91 (2.12–3.69) At 36 mo: 3.80 (NA)	Landmark study focusing on HPV DNA testing versus VIA as primary screening methods for screen-and-treat strategy, which fits the situation of low-resource settings. The cumulative detection rates are reported here for each follow-up
Sankaranarayanan et al. (2005, 2009) India	Cluster-RCT design. More than 130 000 healthy women, married but not pregnant, aged 30–59 yr with an intact uterus and no past history of cervical neoplasia, previously unscreened, in rural communities of Osmanabad District, India, were recruited in 1999–2003 and followed up until 2007. Recruited women were randomly assigned to HPV DNA test, VIA, cytology, or control group	CIN2/3: 0.9 (0.6–1.4), 245/27 192 Cervical cancer: 0.2 (0.1–0.4), 73/27 192 CIN2+: 1.2, 318/27 192	CIN2/3: 0.7 (0.3–1.5), 195/26 765 Cervical cancer: 0.3 (0.0–0.7), 82/26 765 CIN2+: 1.0, 277/27 192	Both articles provided the baseline results. Given that Sankaranarayanan et al. (2009) provided more comprehensive information, the main results presented here are based on this article

Table 4.25   (continued)

Reference Country	Study description	Detection rates for different disease end-points (%) (95% CI), *n/N*		Comments
		HPV	**VIA**	
Sarian et al. (2010) Eastern Europe and Latin America	Data were pooled from both the NIS cohort (*n* = 3187) and the LAMS (*n* = 12 114). Women in the NIS cohort attended 6 outpatient clinics in the Russian Federation, Belarus, and Latvia in 1998–2002, and had a mean age of 32.6 yr (range, 15–85 yr). All women underwent Pap testing and HPV DNA testing (HC2). Women in the LAMS cohort had a mean age of 37.9 yr (range, 14–67 yr) and were examined by cytology and VIA, VILI, cervicography, and HPV DNA test (HC2) at 4 clinics in Brazil and Argentina	CIN2+: 2.3, 169/7498	CIN2+: 0.7, 83/12 093	
Asthana & Labani (2015) India	Cross-sectional design. 4658 ever-married women aged 30–59 yr with no history of CIN or cervical cancer, hysterectomy, or the presence of any associated condition were recruited from rural areas in Uttar Pradesh, India, in 2011–2012. All women were screened with HPV DNA test with self-collected sample, HPV DNA test with clinician-collected sample, cytology, and VIA. All screen-positive women were referred for colposcopy and directed biopsy	CIN2+: Self-collected: 2.7 (1.2–4.2) per 1000 women screened Clinician-collected: 3.6 (1.8–5.4) per 1000 women screened CIN3+: Self-collected: 1.5 (0.37–2.6) per 1000 women screened Clinician-collected: 2.4 (0.97–3.8) per 1000 women screened	CIN2+: 1.5 (0.37–2.6) per 1000 women screened CIN3+: 0.21 (−0.21 to 0.63) per 1000 women screened	
Basu et al. (2015) India	Cross-sectional design. 39 740 apparently healthy women aged 30–60 yr from rural districts adjacent to the metropolitan city of Kolkata in eastern India were recruited in 2010–2014. All women were screened with HPV DNA test and VIA	CIN2+: 5.1 per 1000 women screened CIN3+: 3.8 per 1000 women screened	CIN2+: 4.8 per 1000 women screened CIN3+: 2.8 per 1000 women screened	

Table 4.25   (continued)

Reference Country	Study description	Detection rates for different disease end-points (%) (95% CI), *n/N*		Comments
		HPV	**VIA**	
Zhao et al. (2018) China	Cross-sectional study design. 33 823 women aged 35–64 yr, with an intact uterus and with no history of cervical neoplasia or cervical cancer, who were not pregnant and had no suspicious symptoms, and who understood the process and were willing to participate were recruited from rural areas across 7 large geographical regions in China in 2015–2018. In rural areas, women were randomized to initial screening with HPV test (*n* = 15 577), cytology (*n* = 7089), or VIA (*n* = 11 157)	CIN2+: 0.61, 95/15 577	CIN2+: 0.49, 55/11 157	This study is based on real-world data generated from both rural areas (*n* = 33 823) and urban areas (*n* = 30 108) across 7 large geographical regions in China. The results presented here only represent the data from rural areas, because VIA was not applied in urban areas. Women were initially randomized with a 1:1:1 ratio to the 3 arms; however, cytology was not applicable for some rural areas, so VIA was used instead, resulting in more VIA-screened women than HPV-screened and cytology-screened women

CIN, cervical intraepithelial neoplasia; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HC2, Hybrid Capture 2; HPV, human papillomavirus; LAMS, Latin American Screening Study; mo, month or months; NA, not available; NIS, New Independent States; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine; yr, year or years.

free of CIN2+ at 6 months were followed up at 12 months and 36 months. At the 12-month follow-up, the cumulative prevalence of CIN2+ was 1.42% (95% CI, 0.87–1.97%) in the HPV-and-treat group, 2.91% (95% CI, 2.12–3.69%) in the VIA-and-treat group, and 5.41% (95% CI, 4.32–6.50%) in the control group in the 2708 women examined. This corresponds to a reduction of 74% in the HPV-and-treat group and of 46% in the VIA-and-treat group compared with the control group (Denny et al., 2005). At the 36-month follow-up, the cumulative detection rate of CIN2+ was lower in the HPV-and-treat group (1.5%) than in the VIA-and-treat group (3.8%), whereas the rate was 3.6% in the control group. This corresponds to a reduction of 72.5% (95% CI, 60.1–85.0%) in CIN2+ in the HPV-and-treat group and a reduction of 32.0% (95% CI, 11.1–52.8%) in CIN2+ in the VIA-and-treat group compared with the control group at 36 months (Denny et al., 2010). In addition, the incidence of CIN2+ detected more than 12 months after enrolment was 0.3% (95% CI, 0.05–1.02%) in the HPV-and-treat group, which was significantly less than in the VIA-and-treat group (1.3%; 95% CI, 0.8–2.1%) and in the control group (1.0%; 95% CI, 0.5–1.7%) (*P* = 0.003) (Denny et al., 2010).

A study involving 33 823 women living in rural areas across seven large geographical regions in China reported detection rates of CIN2+ of 0.61% (95 of 15 577) with HPV DNA testing (*care*HPV, cobas 4800, or Liferiver hrHPV genotyping) and 0.49% (55 of 11 157) with VIA or VILI (Zhao et al., 2018).

In a cross-sectional study in rural India, 4658 eligible women were screened with HPV DNA testing (*care*HPV) with clinician-collected and self-collected samples, VIA, and cytology. For HPV DNA testing with clinician-collected samples, detection rates of CIN2+ were 3.6 (95% CI, 1.8–5.4) per 1000 women screened and detection rates of CIN3+ were 2.4 (95% CI, 0.97–3.8) per 1000 women screened. For HPV DNA testing on self-collected samples, detection rates of CIN2+

were 2.7 (95% CI, 1.2–4.2) per 1000 women screened and detection rates of CIN3+ were 1.5 (95% CI, 0.37–2.6) per 1000 women screened. For VIA, detection rates of CIN2+ were 1.5 (95% CI, 0.37–2.6) per 1000 women screened and detection rates of CIN3+ were 0.21 (95% CI, −0.21 to 0.63) per 1000 women screened (Asthana & Labani, 2015).

A demonstration project in eastern India reported detection rates of CIN2+ of 5.1 per 1000 women screened with HPV DNA testing and 4.8 per 1000 women screened with VIA. For CIN3+, the detection rate with HPV DNA testing (3.8 per 1000 women screened) was significantly higher (*P* = 0.016) than that with VIA (2.8 per 1000 women screened) (Basu et al., 2015).

In a pooled analysis focused on studies in eastern Europe and Latin America, the estimated detection rate of CIN2+ was 2.3% (169 of 7498) in the HPV DNA testing group and 0.7% (83 of 12 093) in the VIA group (Sarian et al., 2010).

(d) Changes in cervical cancer incidence and mortality rates

Only the RCT in Osmanabad District in India has assessed the effect of a single round of HPV DNA testing and VIA as primary screening methods on cervical cancer incidence and mortality rates (Sankaranarayanan et al., 2005, 2009) (Table 4.26). During a follow-up of 8 years, a total of 127 cases of cervical cancer were diagnosed in the HPV DNA testing arm (age-standardized incidence rate [ASIR], 47.4 per 100 000 person-years), compared with 157 cases in the VIA arm (ASIR, 58.7 per 100 000 person-years). A single round of screening with HPV DNA testing also dramatically reduced the incidence of cervical cancer of FIGO stage II or higher compared with VIA screening. The burden of cervical cancer of stage II or higher was reported as 39 cases in the HPV DNA testing arm (ASIR, 14.5 per 100 000 person-years), compared with 86 cases in the VIA arm (ASIR, 32.2 per 100 000 person-years). Fewer cases of cervical cancer

Table 4.26 Age-standardized incidence and mortality rates of cervical cancer with HPV testing versus visual inspection with acetic acid (VIA)

Reference Country	Study description	Age-standardized incidence rate of all cervical cancer (per 100 000 person-years)		No. of cases of cervical cancer of stage II or higher/total no. of cases of cervical cancer (%)		Age-standardized incidence rate of cervical cancer of stage II or higher (per 100 000 person-years)		No. of cases of invasive cervical cancer among screening-negative women/total no. of screening-negative women		Deaths from cervical cancer/total no. of cases of cervical cancer (%)		Age-standardized mortality rate of cervical cancer (per 100 000 person-years)	
		HPV	VIA	HPV	VIA	HPV	VIA	HPV	VIA	HPV	VIA	HPV	VIA
Sankaranarayanan et al. (2005, 2009) India	See Table 4.25	47.4	58.7	39/127 (30.7%)	86/157 (54.8%)	14.5	32.2	8/24 380 (0.033%)	25/23 032 (0.109%)	34/127 (26.8%)	56/157 (35.7%)	12.7	20.9

HPV, human papillomavirus; VIA, visual inspection with acetic acid.

developed in HPV DNA-negative women (8 cases in 24 380 women; ASIR, 3.7 per 100 000 person-years) than in VIA-negative women (25 cases in 23 032 women; ASIR, 16.0 per 100 000 person-years). Lower cervical cancer-related mortality was also observed in the HPV DNA testing arm. There were 34 deaths in the HPV DNA testing arm (age-standardized mortality rate [ASMR], 12.7 per 100 000 person-years), compared with 56 deaths in the VIA arm (ASMR, 20.9 per 100 000 person-years) (Sankaranarayanan et al., 2009).

(e) Harms

Diagnostic harms can be inferred by the colposcopy referral rates and the PPVs of the screening tests. Details of studies reporting colposcopy referral rates and/or PPVs for HPV DNA testing and VIA are given in Table 4.27. For HPV DNA testing compared with VIA, the different studies did not consistently report a higher or lower proportion of colposcopy referrals or a larger number of colposcopies needed to detect one CIN2+ or CIN3+ case. PPVs were generally higher with HPV DNA testing than with VIA.

4.4.4 Comparison of HPV DNA testing alone versus co-testing

(a) Introduction

Co-testing as a primary screening modality consists of analysing samples for both cytology and HPV at the same time, regardless of the corresponding test result. The analyses can be conducted on the same sample in the case of LBC, where the residual sample can be tested for HPV, or on separate samples taken in sequence at the same visit. The clinical decision about follow-up and/or referral is then made on the basis of the combination of the test results.

The introduction and broader use of LBC since the 2005 *IARC Handbook* has facilitated the use of co-testing in guidelines and routine practice. The technical implementation of co-testing follows the use of cytology and HPV testing as previously described (see Sections 4.3.1 and 4.4.1, respectively). A range of test technologies and analysis platforms exist for both HPV testing and cytology. The interoperability of these sampling methods and platforms enables co-testing but varies across settings and manufacturers.

Studies examining co-testing range from classic RCTs to implementation studies and retrospective analyses of screening test results before precancer and cancer diagnosis. The time perspective for these studies varies: some studies look at the first round of screening results for detection rates and test performance, whereas others present longitudinal evidence for the comparison of cumulative incidence by baseline test results. The early RCTs that compared HPV testing with cytology enabled analyses of co-testing because cytology was done in every participant. In the main results reported by these trials, HPV testing alone was compared with cytology, but the follow-up data provided comparisons between cytology, HPV testing, and co-testing screening strategies (Bulkmans et al., 2004; Naucler et al., 2007; Ronco et al., 2007a; Kitchener et al., 2009a).

In this review, meta-analyses and joint analyses of cohort studies were examined, as well as studies that directly evaluated disease outcomes or test performance of HPV testing alone compared with co-testing as a primary screening modality. Modelling studies, cost–effectiveness analyses, and studies that evaluated co-testing as a follow-up strategy or in conjunction with other biomarkers were excluded. Studies that examined co-testing in specific populations (e.g. non-attenders), as a test of cure, or as a screening programme exit test were also excluded.

Table 4.27 Comparison of potential diagnostic harms of HPV DNA testing versus VIA

Reference	Study description	Colposcopy referrals Referral rate (%) (95% CI), *n/N*		PPV for different disease end-points (%) (95% CI), *n/N*	
		HPV	**VIA**	**HPV**	**VIA**
Sankaranarayanan et al. (2009)	See Table 4.25	10.3, 2812/27 192	13.9, 3733/26 765	CIN2/3: 11.3, 318/2812 Cancer: 2.6, 73/2812	CIN2/3: 7.4, 277/3733 Cancer: 2.2, 82/3733
Longatto-Filho et al. (2012)	LAMS cohort study. > 12 000 women at 4 clinics in Brazil and Argentina. Large sample size with both cross-sectional and prospective cohorts, which covered regions with different cervical cancer incidence rates. All women were screened with cytology, VIA, VILI, HPV DNA test (HC2) with self-collected sample and clinician-collected sample. Women with a positive screening test result were referred for colposcopy	NA	NA	CIN2+: Self-collected: 9.1 (3.0–22.6) Clinician-collected: 7.9 (6.0–10.1)	CIN2+: 6.1 (4.9–7.6)
Zhao et al. (2013)	START-UP project. 7421 women aged 25–65 yr in 3 counties of China (Yangcheng, Xinmi, and Tonggu) were recruited and tested with *care*HPV, HC2, HPV E6, and VIA using both self-collected and clinician-collected samples. Women with a positive screening test result were referred for colposcopy with directed biopsy. In addition, a randomly selected 10% of women with a negative test result for all the tests also underwent colposcopy	*care*HPV: Self-collected: 14.5 Clinician-collected: 14.4 HC2: Self-collected: 17.9 Clinician-collected: 14.5	7.3	CIN2+: *care*HPV: Self-collected: 11.1 (9.3–13.1) Clinician-collected: 13.0 (11.1–15.2) HC2: Self-collected: 10.0 (8.4–11.7) Clinician-collected: 12.9 (10.9–15.0) CIN3+: *care*HPV: Self-collected: 7.7 (6.2–9.5) Clinician-collected: 9.1 (7.4–10.9) HC2: Self-collected: 6.8 (5.5–8.3) Clinician-collected: 9.0 (7.3–10.8)	CIN2+: 12.7 (10.0–15.9) CIN3+: 9.4 (7.0–12.2)

Table 4.27 (continued)

Reference	Study description	Colposcopy referrals Referral rate (%) (95% CI), *n/N*		PPV for different disease end-points (%) (95% CI), *n/N*	
		HPV	VIA	HPV	VIA
Asthana & Labani (2015); Labani & Asthana (2016)	See Table 4.25	Self-collected: 2.4 (2.0–2.8), 111/4658 Clinician-collected: 2.9 (2.9–3.4), 136/4658	5.5 (4.9–6.2), 257/4658	CIN2+: Self-collected: 11.7 (6.3–19.1) Clinician-collected: 12.5 (7.4–9.1) CIN3+: Self-collected: 6.3 (2.6–12.6) Clinician-collected: 8.1 (4.1–13.9)	CIN2+: 2.7 (1.1–5.5) CIN3+: 0.4 (0.0–2.2)
Holt et al. (2017)	Postmenopausal women (see Table 4.24 for details)	17.2 (15.9–18.7), 475/2757	6.2 (5.3–7.1), 170/2757	CIN2+: 17.3 (14.1–20.9), 82/475 CIN3+: 9.9 (7.4–12.8), 47/475	CIN2+: 15.3 (10.5–21.3), 26/170 CIN3+: 11.8 (7.5–17.3), 20/170
Wang et al. (2019)	Cross-sectional design. 2668 women aged ≥ 18 yr in Inner Mongolia, China, were screened with HPV DNA test and VIA concurrently. Women with a positive test result were referred for colposcopy	17.5 (16.1–19.0), 467/2668	8.1 (7.1–9.2), 216/2668	CIN2+: 5.6 (3.8–8.0), 26/467	CIN2+: 6.0 (3.6–10.0), 13/216

CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HC2, Hybrid Capture 2; LAMS, Latin American Screening Study; PPV, positive predictive value; START-UP, Screening Technologies to Advance Rapid Testing for Cervical Cancer Prevention–Utility and Program Planning; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine; yr, year or years.

(b) Screening performance

A joint database analysis of HPV screening studies included seven studies in six European countries (Dillner et al., 2008) and aimed to estimate the long-term predictive values of HPV-based screening for CIN3+. This analysis included 24 295 women who were screened with HPV testing and cytology at baseline and had at least one additional cervical cytology or histopathology examination during follow-up. The studies differed with respect to the ages of women included, the HPV tests used, and the setting. The cumulative incidence of CIN3+ over 72 months of follow-up was examined by baseline test results, and the test characteristics were reported for cytology, HPV testing, and co-testing with cytology and HPV testing (at least one positive). The cumulative incidence of CIN3+ at 72 months for HPV-negative women was 0.27% (95% CI, 0.12–0.45%), which was similar to that for co-test-negative women at the same time point. At 72 months, the sensitivity of HPV testing for CIN3+ was 90% (95% CI, 80–95%) and the specificity was 88.28% (95% CI, 87.83–88.70%) [recalculated by the Working Group using absolute values without any adjustment; this was erroneously given in the publication]. The corresponding values at 72 months for co-testing with cytology and HPV testing were 92% (95% CI, 84–96%) and 87% (95% CI, 81–93%), respectively.

In a meta-analysis, co-testing with cytology and HC2 testing produced higher detection of CIN2+ (42%; 95% CI, 36–48%) and CIN3+ (33%; 95% CI, 29–37%) compared with cytology alone, and the specificity for the same outcomes was 6% (95% CI, 6–7%) and 8% (95% CI, 7–9%) lower, respectively. When cytology was added to HC2 testing and compared with HPV testing alone, the average sensitivity increased by 5% (95% CI, 4–7%) for CIN2+ and by 2% (95% CI, 1–3%) for CIN3+, and the specificity decreased significantly (ratio for CIN2+, 0.95; 95% CI,

0.94–0.96 and ratio for CIN3+, 0.93; 95% CI, 0.92–0.95). The pooled estimates from the trials showed a non-significant increase in sensitivity for co-testing compared with HPV alone (detection rate ratio for CIN2+, 1.06; 95% CI, 0.97–1.16 and detection rate ratio for CIN3+, 1.04; 95% CI, 0.92–1.17) (Arbyn et al., 2012). [The studies outlined below, which have been conducted since this meta-analysis was completed, used different HPV and cytology platforms but came to broadly the same conclusion.]

(c) Effectiveness

(i) RCTs

RCTs examining the performance of co-testing are outlined in Table 4.28.

Four RCTs in Europe were identified that compared hrHPV co-testing with cytology alone: the NTCC trial in Italy (Ronco et al., 2007a, 2010, 2014), the POBASCAM trial in the Netherlands (Bulkmans et al., 2004; Rijkaart et al., 2012a; Dijkstra et al., 2016), the SwedeScreen trial in Sweden (Naucler et al., 2007; Elfström et al., 2014), and the ARTISTIC trial in the United Kingdom (Kitchener et al., 2009a, b, 2014). The primary results of these trials are reviewed in Section 4.4.2, and long-term follow-up data from these studies have been pooled and provide evidence on the comparison of testing methods and the effectiveness against invasive cervical cancer as an outcome (Arbyn et al., 2012; Ronco et al., 2014).

Both Dijkstra et al. (2016) and Elfström et al. (2014) examined the cumulative incidence of high-grade lesions (CIN2+ or CIN3+). Dijkstra et al. (2016) concluded that the difference between hrHPV testing and hrHPV co-testing with cytology became less pronounced as follow-up time increased, and Elfström et al. (2014) concluded that the difference was minimal over time. Elfström et al. (2014) also calculated the test performance over different follow-up periods (3, 5, 8, and 10 years) and found that although the

Table 4.28 Randomized controlled trials and cohort studies comparing co-testing versus HPV DNA testing

Reference	Study population	Screening exposure Age of included subjects (years)	End-point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Detection rate	Incidence
Randomized controlled trials							
Mayrand et al. (2007)	10 154 women who sought screening tests for cervical cancer in any of 30 clinics in Montreal and St. John's, Canada	HPV DNA test and cytology 30–69 Pap test result of ASC-US+, or HPV test result of ≥ 1 pg HPV DNA/mL	CIN2+	100.0	92.5	NA	NA
Elfström et al. (2014)	12 527 women who attended the organized cervical screening programme in Sweden. 13-year follow-up of the SwedeScreen RCT of primary HPV screening	HPV DNA test and cytology 32–38	CIN2+	Co-testing: 3-yr: 96.69 (90.25–98.93) 5-yr: 91.22 (84.84–95.07) 8-yr: 82.67 (75.79–87.91) 10-yr: 77.19 (70.16–82.97) HPV testing: 3-yr: 92.23 (84.58–96.25) 5-yr: 86.40 (79.21–91.37) 8-yr: 77.30 (69.95–83.29) 10-yr: 72.45 (65.17–78.71)	Co-testing: 3-yr: 90.32 (89.54–91.05) 5-yr: 90.73 (89.97–91.45) 8-yr: 90.98 (90.22–91.69) 10-yr: 91.10 (90.34–91.81) HPV testing: 3-yr: 94.05 (93.42–94.63) 5-yr: 94.47 (93.85–95.03) 8-yr: 94.69 (94.08–95.24) 10-yr: 94.82 (94.22–95.37)	NA	Cumulative incidence (%) (95% CI) at 13-yr follow-up (no difference between co-testing and HPV testing): CIN2+: 1.63 (1.11–2.32) in the intervention arm CIN3+: 0.84 (0.48–1.47) in the intervention arm

Table 4.28 (continued)

Reference	Study population	Screening exposure Age of included subjects (years)	End-point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Detection rate	Incidence
Dijkstra et al. (2016)	Of 44 938 women enrolled in the Netherlands, 22 420 were randomized to the intervention group (managed by co-testing results) and 22 518 to the control group (managed only by cytology result)	HPV DNA test and cytology 29–61	CIN3+ and cancer	NA	NA	NA	Incidence ratio (95% CI) (intervention vs control): CIN3+: Cytology-negative and/or HPV-negative: 0.86 (0.63–1.17) Cytology-negative and/or HPV-positive: 0.95 (0.71–1.28) Cytology-positive and/or HPV-negative: 0.62 (0.28–1.37) Cancer: Cytology-negative and/or HPV-negative: 0.58 (0.23–1.48) Cytology-negative and/or HPV-positive: 0.29 (0.10–0.87) Cytology-positive and/or HPV-negative: 5.97 (0.30–119.22)
Han et al. (2020)	182 119 women screened in the primary health-care facilities of 9 districts in Beijing, China, from January 2014 to March 2015	HPV DNA test and cytology 35–64	CIN2+	NA	NA	Co-testing: 5.06 for CIN2+ 1.63 for CIN3+ HPV testing: 3.35 for CIN2+ 2.10 for CIN3+	NA

Table 4.28 (continued)

Reference	Study population	Screening exposure Age of included subjects (years)	End-point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Detection rate	Incidence
Cohort studies							
Cuzick et al. (2003) Mesher et al. (2010) [6-year follow-up][b]	Multicentre screening study of 11 085 women in the United Kingdom associated with 5 referral centres	HPV test and cytology 30–60	CIN2+	Baseline: Co-testing:[b] 100.0 (96.0–100.0) HPV testing (≥ 2 pg/mL): 96.0 (89.7–98.5)	Baseline: Co-testing:[b] 94.0 (93.4–94.5) HPV testing (≥ 2 pg/mL): 94.4 (93.9–95.0)	NA	6-yr cumulative incidence (%): Co-test-negative: 0.21 HPV-negative: 0.28
Petry et al. (2003)[a]	8466 women attending routine cervical cancer screening in Germany	HPV test and cytology ≥ 29	CIN2+ and CIN3+	CIN2+: Co-testing: 100.0 (93.7–100.0) HPV testing: 97.8 (86.3–99.7) CIN3+: Co-testing: 100.0 (93.7–100.0) HPV testing: 97.3 (83.2–99.6)	CIN2+: Co-testing: 93.8 (91.8–95.3) HPV testing: 95.3 (93.5–96.6) CIN3+: Co-testing: 94.9 (93.1–96.2) HPV testing: 95.2 (93.4–96.5)	NA	NA
Katki et al. (2011)	331 818 women enrolled in co-testing at KPNC starting in 2003–2005 (and with adequate enrolment co-test results) and followed up to 31 December 2009	HPV test and cytology ≥ 30	CIN3+	NA	NA	NA	5-yr cumulative incidence (per 100 000 women per year): Co-test-negative: 3.2 HPV-negative: 3.8

Table 4.28   (continued)

Reference	Study population	Screening exposure Age of included subjects (years)	End-point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Detection rate	Incidence
Rijkaart et al. (2012b)[c]	VUSA-Screen study. 25 871 women in the Netherlands offered both cytology and hrHPV testing	HPV test and cytology 29–61	CIN2+ and CIN3+	NA[c]	NA[c]	NA	3-yr cumulative risk of CIN2+ (%) (95% CI): Co-test-negative: 0.24 (0.12–0.64) HPV-negative: 0.26 (0.14–0.69) 3-yr cumulative risk of CIN3+ (%) (95% CI): Co-test-negative: 0.05 (0.01–0.42) HPV-negative: 0.06 (0.02–0.46)
Wright et al. (2015)	42 209 women in the USA who underwent cytology and hrHPV testing	HPV test and cytology ≥ 25	CIN3+	NA	NA	NA	3-yr cumulative incidence (%) (95% CI): Co-test-negative: 0.3 (0.1–0.6) HPV-negative: 0.3 (0.1–0.7)
Choi et al. (2016)	922 women who visited the gynaecology clinic at the Korea University Ansan Hospital, Seoul, Republic of Korea, for routine screening or follow-up during an 18-mo period	HPV test and cytology 17–86 (median, 44.7)	CIN2+ and CIN3+	CIN2+: Co-testing: 72.1 HPV testing: 71.3 CIN3+: Co-testing: 59 HPV testing: 61.7	CIN2+: Co-testing: 96.7 HPV testing: 88.1 CIN3+: Co-testing: 100 HPV testing: 98.5	NA	NA

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; KPNC, Kaiser Permanente Northern California; LSIL, low-grade squamous intraepithelial lesion; mo, month or months; NA, not applicable; RCT, randomized controlled trial; yr, year or years.

[a] The follow-up time was not clearly mentioned in the article.

[b] Positive test results defined as cytology ≥ mild (LSIL) or HPV ≥ 2 pg/mL.

[c] Test characteristics for HPV and cytology were reported separately, not as combined test results, and are therefore not noted here.

sensitivity of co-testing was higher than that of HPV testing alone, the specificity was lower for all follow-up periods. In the long-term follow-up of these two trials, the absolute difference in cumulative incidence between co-testing and HPV testing alone remained constant over time and was minimal.

The CCCaST study in Canada randomized 10 154 women aged 30–69 years to either screening with a focus on the HPV testing result or screening with a focus on the cytology result (both tests were performed in both arms). CIN2+ outcomes were reported by screening results (individual and joint HPV and cytology results and HPV genotype-specific results). The test characteristics reported for HPV testing alone and for co-testing with CIN2+ as the outcome were as follows: the sensitivity of HPV testing alone for CIN2+ was 94.6% (95% CI, 84.2–100%) and the specificity was 94.1% (95% CI, 93.4–94.8%) (using a threshold of 1 pg HPV DNA/mL, i.e. 5000 copies of HPV genome per test), and the sensitivity of co-testing for CIN2+ was 100% and the specificity was 92.5%, where the definition of a positive result was ASC-US+ cytology or an HPV test result of 1 pg HPV DNA/mL or above. These estimates were corrected for verification bias and were based on confirmation of the lesion in an excisional specimen (Mayrand et al., 2006, 2007).

In a quasi-RCT implemented in primary health-care facilities, Han et al. (2020) compared cytology with two intervention arms: (i) hrHPV testing alone with cytology triage and (ii) co-testing; the randomization to the intervention arms was done by district. The overall primary outcome was detection rates of CIN2+ by screening strategy; further outcomes included PPV by strategy for CIN2+ and biopsy rates. Detection rates were 5.06‰ for CIN2+ and 1.63‰ for CIN3+ for co-testing, 3.35‰ for CIN2+ and 2.10‰ for CIN3+ for hrHPV testing alone, and 2.47‰ for CIN2+ and 1.24‰ for CIN3+ for cytology. In this study, referral was

based on partial genotyping. In the co-testing arm, women who were positive for carcinogenic HPV types other than HPV16 or HPV18 and cytology-negative were referred for repeat testing after 1 year, instead of being deemed negative, as they were in the HPV testing arm.

Taken together, the comparison of co-testing versus HPV DNA testing as examined in these RCTs shows a marginally higher sensitivity for outcomes of CIN2+ and CIN3+ with co-testing than with HPV testing alone. The specificity of co-testing was lower than that of HPV testing alone. The cumulative incidence of high-grade lesions by baseline HPV test-negative women or co-test-negative women showed minor differences over time. Co-test-negative women had a slightly lower cumulative incidence of high-grade lesions, but the difference was not significant (Table 4.28).

(ii) Cohort studies

Cohort studies examining the performance of co-testing are outlined in Table 4.28. They include the Hanover and Tübingen (HAT) study in Germany (Petry et al., 2003), the HART study in the United Kingdom (Cuzick et al., 2003, Mesher et al., 2010), the KPNC cohort in the USA (Katki et al., 2011), and the ATHENA study in the USA (Wright et al., 2015), as well as two studies embedded in routine screening, the VUSA-Screen study in the Netherlands (Rijkaart et al., 2012b) and a study in the Republic of Korea (Choi et al., 2016).

The HAT study included 7908 women aged 30 years and older from routine screening in two cities in Germany in 1998–2000 (Petry et al., 2003). Two samples were taken at baseline; one was analysed with conventional cytology and the other with HPV testing. One round of screening was included, and women were followed up depending on the combination of test results at baseline. Test characteristics were estimated for combinations of baseline test results and the outcomes of CIN2+ and CIN3+. For HPV testing

alone, the sensitivity for CIN2+ was 97.8% (95% CI, 86.3–99.7%) and the specificity was 95.3% (95% CI, 93.5–96.6%). For co-testing (with a cytology threshold of ASC-US+, including unsatisfactory results or any hrHPV positivity), the sensitivity was 100.0% (95% CI, 93.7–100.0%) and the specificity was 93.8% (95% CI, 91.8–95.3%). In the co-testing analysis, positivity in either test resulted in referral. For the outcome of CIN3+, the estimates were similar.

The HART study enrolled 11 085 women aged 30–60 years from routine screening in five cities in the United Kingdom in 1998–2001. As in the HAT study, two samples were taken and analysed with conventional cytology and with HPV testing (Cuzick et al., 2003). Comparisons of the performance of HPV testing alone and co-testing were presented both in the baseline results after one round of screening (Cuzick et al., 2003; test characteristics) and in the long-term follow-up based on an average of 6 years of follow-up (Mesher et al., 2010; cumulative incidence of CIN2+ by baseline test result). At baseline, the sensitivity of HPV testing alone (using a threshold of 2 pg/mL) for CIN2+ was 96.0% (95% CI, 89.7–98.5%) and the specificity was 94.4% (95% CI, 93.9–95.0%), whereas the sensitivity of co-testing, in which the definition of a positive result was mild (similar to LSIL) or worse in cytology or ≥ 2 pg/mL by HPV testing, was 100.0% (95% CI, 96.0–100.0%) and the specificity was 94.0% (95% CI, 93.4–94.5%) (Cuzick et al., 2003). The long-term follow-up of the cohort (Mesher et al., 2010) showed the cumulative incidence of CIN2+ in non-overlapping categories of baseline test results, including HPV-negative women and co-test-negative women; 0.28% of women who were HPV-negative at baseline were diagnosed with CIN2+ during follow-up, and 0.21% of women who were co-test-negative (i.e. HPV-negative and cytology-negative) at baseline developed CIN2+ during follow-up.

KPNC adopted a co-testing strategy in 2003. Data from this large cohort including 331 818 women were reported by Katki et al. (2011) and reflect routine clinical practice. Over 5 years of follow-up, the cumulative incidence of cancer was higher for hrHPV-negative women (3.8 per 100 000 women per year) than for co-test-negative (i.e. hrHPV-negative and cytology-negative) women (3.2 per 100 000 women per year). In a further analysis of the KPNC cohort data (Gage et al., 2014), specific proposed screening strategies in the USA were examined; hrHPV testing alone and co-testing at different intervals were compared with respect to risks of CIN2+, CIN3+, and cancer. The main comparison of interest was the risk of CIN3+ or cancer at 3 years for hrHPV-negative women versus the risk at 5 years for co-test-negative women. The risk of CIN3+ was significantly lower in hrHPV-negative women at 3 years than in co-test-negative women at 5 years (0.069% vs 0.11%; $P < 0.0001$). The risk of cancer was also lower in hrHPV-negative women at 3 years than in co-test-negative women at 5 years (0.011% vs 0.014%), although this difference was not statistically significant. Schiffman et al. (2018) also used the KPNC cohort to examine the relative contribution of the cytology component to co-testing, and concluded that the increased sensitivity of co-testing versus HPV testing alone for detection of treatable precancers and early curable cervical cancers affects very few cases.

In the context of the population-based screening programme in the Netherlands, the VUSA-Screen study (Rijkaart et al., 2012b) examined the effectiveness of co-testing with cervical cytology and hrHPV testing. A total of 25 658 women with adequate baseline samples for cytology and HPV testing were included. Histological results stratified by the baseline screening test result were reported. The 3-year cumulative risk of CIN3+ was 0.06% (95% CI, 0.02–0.46%) for HPV-negative women and 0.05% (95% CI, 0.01–0.42%) for both cytology-negative and hrHPV-negative women. Therefore, adding cytology to hrHPV testing was interpreted to have minimal impact on

evaluating the risk of CIN3+. Test characteristics for hrHPV testing and cytology were reported separately, not as combined test results, and are therefore not given here.

The ATHENA study aimed to evaluate hrHPV testing as a primary screening modality in women aged 25 years or older recruited from routine cervical screening (Wright et al., 2015). The screening strategies examined included hrHPV testing alone (with referral for colposcopy for women who were HPV16- and/or HPV18-positive or ASC-US+ in reflex cytology) and a co-testing strategy that corresponded to United States screening recommendations (cytology alone for women younger than 30 years and co-testing for women aged 30 years or older). The cumulative risks of CIN2+ and CIN3+ were measured over 3 years. The cumulative incidence rate of CIN3+ in HPV-negative women was 0.3% (95% CI, 0.1–0.7%), which was the same as in women who were both HPV-negative and cytology-negative (0.3%; 95% CI, 0.1–0.6%).

In a large cohort trial, the clinical performance of primary HPV screening plus LBC co-testing was compared with that of HPV screening alone and LBC alone at a hospital in Seoul, Republic of Korea, in women aged 17–86 years (Choi et al., 2016). For CIN2+, the sensitivity of primary HPV testing alone was 71.3% and of co-testing was 72.1%; the specificity was 88.1% and 96.7%, respectively. For CIN3+, the sensitivity of HPV testing alone was 61.7% and of co-testing was 59%; the specificity was 98.5% and 100%, respectively.

In recent years, a series of retrospective cohort studies have been conducted that examined the screening history of selected screening cohorts and cohorts of women diagnosed with CIN3+, AIS, or cancer. In a laboratory-based study, Blatt et al. (2015) conducted a retrospective cohort analysis examining the co-test results of 256 648 women aged 30–65 years who had complete results for cytology and HPV testing in 2005–2011 and a follow-up cervical biopsy within 1 year of the index test. Test characteristics for

CIN3+ were calculated and reported as follows: the sensitivity of HPV testing alone was 94.0% (95% CI, 93.3–94.7%), and the sensitivity of co-testing was 98.8% (95% CI, 98.6–99.2%). The inclusion criteria required that women had undergone colposcopy and biopsy within 1 year of the index test. By including only women with a follow-up biopsy and limiting the follow-up time to within 1 year, the study excluded a significant percentage of HPV-positive and cytology-negative women who returned for rescreening after more than 1 year; this biased the results in favour of strategies that include cytology at baseline (Castle, 2015; Giorgi Rossi et al., 2016).

Kaufman et al. (2020) took a comparable retrospective approach to analysing co-test results before diagnosis. They examined a total of 13 633 071 co-test results in women aged 30 years or older. Women were included in the analysis if they had at least one LBC and HPV co-test result before a histopathologically confirmed diagnosis of CIN3, AIS, or cancer; 1615 co-tests before 1259 cancer diagnoses and 11 164 co-tests before 8048 CIN3 or AIS diagnoses were included. The results were reported as the proportion of positive results by testing modality before the different diagnoses (cancer was analysed overall and by histopathology), overall and stratified by within 12 months of diagnosis or more than 12 months before diagnosis. In the analysis of test results within 12 months of diagnosis of a cancer, 77.5% of the women were HPV-positive, 85.1% were LBC-positive, and 94.1% were positive on either test. In contrast, the results for more than 12 months before diagnosis show minimal differences between testing modalities. [The focus on test performance within 12 months of a diagnosis presents a significant limitation in the interpretation and application of the results. The authors did not distinguish between screening tests and clinical tests undergone because of symptoms. Tests undergone within a short period of cancer diagnosis often represent tests undergone in the diagnostic workup of a cancer rather than

screening tests; therefore, they are not as indicative of the performance of the testing modality for screening purposes.]

Overall, the performance of HPV testing alone and co-testing in the cohort studies summarized above followed a pattern similar to the results presented in the RCTs: higher sensitivity for co-testing than for HPV testing alone, but lower specificity. The cohort studies presented further data on the risk of high-grade lesions by baseline test result (HPV-negative or co-test-negative). These results confirmed the results of the RCTs and showed little or no difference in cumulative risk between HPV-negative and co-test-negative women over time.

(iii) Harms

In the RCTs reviewed, the PPV for CIN2+ was higher for HPV testing alone than for co-testing. In the long-term follow-up of the SwedeScreen trial, the PPV for CIN2+ was 19.51%, 25.63%, 29.02%, and 31.12% for HPV testing alone at 3, 5, 8, and 10 years, respectively, compared with 13.32%, 17.53%, 20.21%, and 21.56% for co-testing at the same intervals (Elfström et al., 2014). In the CCCaST study, the PPV for CIN2+ was 7.0% for HPV testing alone and 5.5% for co-testing; the colposcopy referral was 6.1% for HPV testing alone and 7.9% for co-testing (Mayrand et al., 2007).

The PPV for HPV testing alone was consistently higher than that for co-testing, although the differences were small. In the joint database analysis of HPV screening studies, the PPV for CIN3+ was 17.1% (95% CI, 12.7–21.4%) for HPV testing alone and 14.7% (95% CI, 9.9–19.0%) for co-testing (Dillner et al., 2008). In the HAT study, the PPV for CIN2+ was 10.9% (95% CI, 8.2–14.2%) for HPV testing alone and 8.6% (95% CI, 6.5–11.3%) for co-testing. The proportion of women referred for colposcopy was 5.2% for HPV testing alone and 6.8% for co-testing (Petry et al., 2003). In the HART study, the PPV for CIN2+ was 15.0% (95% CI, 12.2–18.34%) for

HPV testing alone (using a threshold of 2 pg/mL) and 14.4% (95% CI, 11.8–17.5%) for co-testing (using a threshold of mild [similar to LSIL] or worse in cytology or ≥ 2 pg/mL by HPV testing) (Cuzick et al., 2003). In the ATHENA study, there was no significant difference in the PPV for CIN2+ between HPV testing alone (20.2%; 95% CI, 18.3–22.0%) and co-testing (19.5%; 95% CI, 17.6–21.4%) (Wright et al., 2015). The proportion of women referred for colposcopy was higher for co-testing than for HPV testing alone.

4.4.5 HPV testing on self-collected versus clinician-collected samples

(a) Diagnostic accuracy

The diagnostic accuracy of HPV-based testing for detection of CIN2+ and CIN3+ on specimens collected by self-sampling needs to be assessed separately. Clinician-collected cervical specimens have been the reference standard for detection of CIN2+, because exfoliated cells are more likely to be sampled from the target site than with self-sampling, which may include cells from the vagina. Self-sampling is being considered as an alternative to clinician sampling because it is more convenient for women and there are potential cost savings for the health-care system (Campos et al., 2017, 2020). Using a self-sampling device, a woman can collect a sample at home or at a specific collection point; this avoids a speculum examination and leaves the cervix undisturbed, which may improve visual triage of screen-positive women if this is performed on the same day.

Arbyn et al. (2014) evaluated 36 studies, including 154 556 women, on the accuracy of self-collected samples versus clinician-collected samples when used for HPV testing. In the context of screening, HPV testing on self-collected samples detected, on average, 76% (95% CI, 69–82%) of CIN2+ and 84% (95% CI, 72–92%) of CIN3+. The pooled absolute specificity was 86%

Table 4.29 Relative sensitivity and relative specificity of hrHPV assays on self-collected samples versus clinician-collected samples, by sampling device and storage medium[a]

Covariate	Number of studies	Relative sensitivity (95% CI)	Relative specificity (95% CI)
Sampling device			
hrHPV assay based on signal amplification			
Brush	13	0.84 (0.78–0.90)	0.93 (0.91–0.96)
Swab	7	0.85 (0.78–0.91)	0.93 (0.90–0.95)
Lavage	2	0.84 (0.69–1.04)	0.74 (0.55–0.98)
Tampon	1	0.86 (0.78–0.96)	1.02 (1.00–1.03)
hrHPV assay based on polymerase chain reaction			
Brush	12	0.98 (0.95–1.02)	0.95 (0.91–0.99)
Swab	4	0.98 (0.93–1.03)	0.93 (0.89–0.98)
Lavage	4	0.95 (0.87–1.04)	1.09 (0.91–1.30)
Tampon	0	NA	NA
Storage medium			
hrHPV assay based on signal amplification			
Cell-preserving[b]	3	0.84 (0.78–0.90)	0.93 (0.91–0.96)
Virological[b]	15	0.86 (0.81–0.91)	0.95 (0.92–0.98)
Dry samples	0	NA	NA
Other	1	0.90 (0.71–1.13)	0.92 (0.71–1.21)
hrHPV assay based on polymerase chain reaction			
Cell-preserving	6	1.00 (0.96–1.04)	0.92 (0.88–0.97)
Virological	3	0.97 (0.91–1.04)	0.94 (0.89–0.99)
Dry samples	7	0.96 (0.90–1.02)	1.01 (0.94–1.10)
Other	1	0.95 (0.80–1.13)	1.05 (0.69–1.58)

CI, confidence interval; hrHPV, high-risk human papillomavirus; NA, not available.

[a] Relative values were computed using a bivariate normal model, separating studies using an hrHPV assay based on signal amplification or an hrHPV assay based on polymerase chain reaction. Pooling was performed using a bivariate normal model.

[b] When the bivariate model containing covariates did not fit or when the number of studies was < 4, a separate pooling of the relative sensitivity and relative specificity using a model for ratios of proportions was run.

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(95% CI, 83–89%) for CIN2+ and 87% (95% CI, 84–90%) for CIN3+ (Arbyn et al., 2014).

An updated analysis was performed (Arbyn et al., 2018) that included 56 diagnostic accuracy studies up to April 2018 (Table 4.29). Studies were included if the following criteria were met: information was provided on a vaginal sample collected by the woman herself (self-collected sample) followed by a cervical sample collected by a clinician (clinician-collected sample); the same hrHPV assay was performed on both samples; all HPV tests evaluated had been clinically validated according to the Meijer guidelines (Meijer et al., 2009); and the presence or absence of CIN2+ was verified by colposcopy and biopsy in all enrolled women or in women with one or more positive test results. Studies with cytology follow-up for women with negative colposcopy results at baseline assessment were also included but were indexed for sensitivity analyses. Standard methods were used for pooling diagnostic test accuracy (Harbord et al., 2007; Harbord & Whiting, 2009). Indicators included the relative accuracy of tests on self-collected samples versus clinician-collected samples, estimated by incorporating assay category as a covariate in the model. The variation of the accuracy was also evaluated according to the

clinical setting (screening population, high-risk population, follow-up for previous abnormalities, and monitoring after treatment), assay, self-sampling device, and storage medium. [Although the pooled absolute sensitivity and specificity for outcomes CIN2+ and CIN3+ varied by clinical setting, relative values were considered adequate for comparison and were presented first for a screening situation and then for a combination of all clinical settings using only relative indicators.] The relative accuracy of hrHPV assays on self-collected samples versus clinician-collected samples did not vary substantially by clinical setting. The overall relative pooled sensitivity was 0.85 (95% CI, 0.80–0.89) for CIN2+ and 0.86 (95% CI, 0.76–0.98) for CIN3+, and the relative pooled specificity was 0.96 (95% CI, 0.93–0.98) for CIN2+ on self-collected samples versus clinician-collected samples. A higher test positivity and lower PPVs tended to be observed for self-collected samples compared with clinician-collected samples when assays based on signal amplification were used. This was not observed when PCR-based assays were used. PCR-based hrHPV assays were equally sensitive (ratio, 0.99; 95% CI, 0.97–1.02) and slightly less specific (ratio, 0.98; 95% CI, 0.97–0.99) for CIN2+ on self-collected samples versus clinician-collected samples, with similar test positivity and non-significantly lower PPVs.

(b)   Additional studies

Since the review by Arbyn et al. (2018), additional studies have been identified that evaluated the accuracy of hrHPV testing for the detection of CIN2+ with vaginal samples and with cervical samples. El-Zein et al. (2018) reported on the Cervical And Self-Sample In Screening (CASSIS) study, which recruited 1217 women aged 21–74 years in Montreal, Canada, attending colposcopy clinics because of an abnormal cytology result. Participants provided three consecutive samples: two different self-collected samples, using the HerSwab device and the

cobas 4800 HPV swab, and a clinician-collected sample. The self-collection devices are designed to be anatomically comfortable to enable women to self-collect a sample of exfoliated cervicovaginal cells; the clinician-collected sample was collected with either a swab or a simple brush. [The Working Group did not find the relevant information to confirm whether the clinician collection was performed with a brush or a swab.] The order of the self-sampling devices was assigned randomly. Of 1076 women with complete information (per-protocol population), HPV positivity was high and comparable between the three devices, ranging from 47.4% to 50.5%. Overall, 152 cases of CIN2+ were detected in the per-protocol analysis and 166 in the intention-to-treat analysis.

The relative sensitivity and the relative specificity of self-sampling with the HerSwab device versus clinician sampling for ASC-US+ were 0.94 and 1.07, respectively. The relative sensitivity and the relative specificity of self-sampling with the cobas swab versus clinician sampling for ASC-US+ were 0.94 and 1.02, respectively; the differences were not statistically significant. [The Working Group noted that all women in the study were referred because of an abnormal test result; this may indicate that most women were likely to have a high HPV viral load, and thus the study population may not be suitable for an evaluation of accuracy between tests applied to screening settings.]

In a randomized non-inferiority trial, Polman et al. (2019b) evaluated the diagnostic accuracy of HPV testing on self-collected samples versus clinician-collected samples for the detection of CIN2+ and CIN3+ in a screening population of women aged 29–61 years in the Netherlands. Samples were tested for carcinogenic HPV types using GP5+/6+ PCR EIA. Of the 187 473 women invited to participate, 8212 were randomly allocated to self-sampling first (group A) and 8198 to clinician sampling first (group B) [The response rate was very low,

because self-sampling was an opt-in option of how to be screened.] A total of 7643 women were included in group A and 6282 in group B. A total of 569 (7.4%) self-collected samples and 451 (7.2%) clinician-collected samples tested positive for HPV (RR, 1.04; 95% CI, 0.92–1.17). The sensitivity and specificity of HPV testing for CIN2+ and CIN3+ did not differ between self-collected and clinician-collected samples: for CIN2+, the relative sensitivity was 0.96 (95% CI, 0.90–1.03) and the relative specificity was 1.00 (95% CI, 0.99–1.01), and for CIN3+, the relative sensitivity was 0.99 (95% CI, 0.91–1.08) and the relative specificity was 1.00 (95% CI, 0.99–1.01). [Note that HPV-positive women in both groups were cross-retested with the other collection method, which was done before colposcopy, but the HPV cross-testing results were not disclosed to study participants and were not used for screening management. Although the study had low participation in regular users of screening, the sample size was high in both arms and the study design was powerful.]

In a small cross-sectional study in 104 women aged 25 years or older in Manchester, United Kingdom, attending a colposcopy clinic for management of abnormal cervical screening, Sargent et al. (2019) evaluated the diagnostic accuracy on self-collected vaginal samples and urine and clinician-collected cervical samples for the detection of CIN2+. Vaginal samples and cervical samples were tested using the cobas 4800 and RealTi*me* HPV assays. CIN2+ was detected in 18 women. The sensitivity for detection of CIN2+ was similar for vaginal samples and cervical samples with both HPV assays [relative sensitivity, 1.01] (RealTi*me* assay: 89%, 16 of 18; cobas 4800 assay: 88%, 15 of 17).

(c)   Longitudinal evaluation of self-sampling

In the Shanxi Province Cervical Cancer Screening Study I, in China, 1997 non-pregnant women aged 35–45 years with no history of cervical cancer or hysterectomy were enrolled in 1999 via cluster sampling (Zhang et al., 2018). At enrolment, all the women underwent HPV testing on a self-collected sample and a clinician-collected sample. All the women had histologically confirmed results at baseline. HPV testing was done using a signal amplification test (HC2). The relative sensitivities for CIN2+ in clinician-collected samples versus self-collected samples were 1.17 (95% CI, 1.07–1.29) at baseline and 1.15 (95% CI, 1.07–1.25) at 6 years. The values of specificity were identical at baseline and at 6 years (RR, 0.99; 95% CI, 0.97–1.00). Data at 16 years provided similar values.

Issues related to the acceptability of and participation in self-sampling are reviewed in Section 3.3.2.

Aitken et al. (2019) reported on the nationwide implementation of hrHPV-based screening in the Netherlands. In this programme, women receive an invitation to have a cervical sample taken by the provider, but they can also opt for self-sampling at home. Data from the first 18 months of the hrHPV-based screening programme were compared with the previous, cytology-based programme with respect to participation, referral, and detection of CIN. About 8% (36 295 of 454 573) of the women had opted for the use of a self-sampling device. Although no increase in participation could be related to self-sampling, CIN2+ detection was higher in self-collected samples than in clinician-collected samples (1.4% vs 1.1%; *P* < 0.001).

(d)   Use of HPV RNA tests on vaginal self-collected samples

The 2018 meta-analysis that assessed the relative accuracy of HPV tests on self-collected versus clinician-collected samples also included three studies in which HPV testing was done with an RNA test (Aptima) (Arbyn et al., 2018). The sensitivity of HPV RNA testing for CIN2+ was significantly lower on self-collected samples than on clinician-collected samples (relative sensitivity, 0.69; 95% CI, 0.52–0.92), whereas the

specificity for CIN2+ was similar in both specimens (relative specificity, 0.97; 95% CI, 0.92–1.02).

Two additional studies evaluated the use of an HPV RNA test (Aptima) on vaginal self-collected samples. Senkomago et al. (2018) studied 350 female sex workers aged 18–50 years in 2009–2013 and compared HPV RNA detection on clinician-collected samples versus self-collected samples. A total of 22 cases with confirmed CIN2+ were detected over a period of 24 months; 18 (82%) were HPV RNA-positive on the clinician-collected samples, and 17 (77%) were HPV RNA-positive on the self-collected samples at baseline [relative sensitivity, 0.85 (95% CI, 0.41–1.76)]. [Note that the referral for biopsy and histological confirmation was done solely on the basis of cytology results, not by HPV test results.] Islam et al. (2020), from the same group, published additional data on HPV RNA testing (Aptima) on dry and wet self-collected samples and found similar performance [the outcome was cytology-confirmed HSIL+].

4.4.6 Comparison of HPV RNA testing versus HPV DNA testing

(a) Use of HPV RNA tests in primary cervical cancer screening

A 2015 review (Arbyn et al., 2015) evaluated the sensitivity and specificity for the detection of CIN2+ and CIN3+ of diverse HPV DNA and RNA assays applied in primary cervical cancer screening and compared them with those of reference HPV DNA tests (HC2 and GP5+/6+ PCR EIA). Six studies that included populations from primary screening were identified that used a 14-HPV type target RNA test (Aptima) and one study that used a 5-HPV type RNA test (PreTect HPV-Proofer). There was no indication that the sensitivity for CIN2+ of the 14-HPV type RNA test was different from that of the comparator HPV DNA test, but it had a higher specificity; the relative sensitivity was 0.98 (95% CI, 0.95–1.01) and the relative specificity was 1.04 (95% CI,

1.02–1.07). The 5-HPV type RNA test was found to be less sensitive but more specific than the comparator HPV DNA test; the relative sensitivity for CIN2+ was 0.74 (95% CI, 0.63–0.88) and the relative specificity was 1.12 (95% CI, 1.10–1.13).

Since that 2015 systematic review, additional studies have been identified that compared the clinical cross-sectional accuracy of an HPV RNA test (Aptima) (Iftner et al., 2015; Maggino et al., 2016; Muangto et al., 2016; Cook et al., 2017) in cervical screening with that of clinically validated hrHPV DNA tests. Other studies aimed to evaluate the longitudinal NPV (Cook et al., 2018; Forslund et al., 2019; Iftner et al., 2019; Zorzi et al., 2020).

In the study of Iftner et al. (2015), 10 040 women aged 30–60 years from the routine cervical cancer screening population of three German centres, in Tübingen, Saarbrücken, and Freiburg, were invited to participate, and 9451 of them were included in the analysis. The study detected 90 cases of CIN2+ and 43 cases of CIN3+. There was no evidence of a difference in the sensitivity for the detection of CIN2+ between the HPV RNA test (Aptima) (87.8%; 95% CI, 80.2–95.5%) and the HPV DNA test (HC2) (93.2%; 95% CI, 87.1–99.2%) [relative sensitivity, 0.94], but the specificity for the detection of CIN2+ of the HPV RNA test was significantly higher than that of the HPV DNA test. For the detection of CIN3+, the sensitivity values were 90.9% for the RNA test and 100.0% for the DNA test [relative sensitivity, 0.90]. For the detection of CIN2+, the specificity values were 96.1% for the RNA test and 94.9% for the DNA test [relative specificity, 1.01]. Women with negative screening test results at baseline were invited to a second round of screening in 2019, and 3295 of them (82.4%) attended follow-up (Iftner et al., 2019). In the second round, 3057 women (92.8%) tested negative by all three screening tests (DNA, RNA, and cytology). A total of 140 women (4.6%) had at least one positive test result at follow-up, and

115 (82%) of those women underwent a colposcopic examination. The 6-year cumulative risks of CIN2+ were 0.62% (95% CI, 0.24–1.59%) for HPV RNA-negative women and 0.47% (95% CI, 0.27–0.81%) for HPV DNA-negative women, and the 6-year cumulative risks of CIN3+ were 0.31% (95% CI, 0.17–0.57%) for HPV RNA-negative women and 0.22% (95% CI, 0.10–0.49%) for HPV DNA-negative women. In women who tested negative by both HPV tests at baseline, the cumulative risk of CIN3+ was 0.17% (95% CI, 0.04–0.75%). The relative sensitivity for the detection of CIN3+ of the HPV RNA test compared with the HPV DNA test was 0.91 [(95% CI, 0.8–1.03)]. [The Working Group noted that the relative risk of CIN3+ between the two cohorts was not provided, and it was estimated to be 1.43, with the 95% confidence interval including unity.]

Cook et al. (2017, 2018) evaluated an HPV RNA test (Aptima) against an HPV DNA test (HC2) within the HPV FOCAL trial. The screening efficacy in women aged 25–65 years of an HPV DNA test (HC2) with LBC triage of all HPV DNA-positive women was compared with LBC screening with HPV DNA triage of women with an ASC-US result. HPV RNA and HPV DNA tests were compared at the baseline screen (3473 women). With HPV DNA as the comparator test, the relative sensitivity of the HPV RNA test for the detection of CIN2+ was 0.96 and for the detection of CIN3+ was 1.00, and the relative specificity was 1.01. In an updated follow-up at 48 months, HPV RNA and HPV DNA tests were compared within the intervention arm (women who tested positive with the HC2 test were triaged with LBC) at baseline and at 48 months for the detection of CIN2+. Women with < CIN2 irrespective of the HPV DNA test result at 48 months were screened with the HPV RNA test, the HPV DNA test, and LBC. At 48 months, 4.8% were HPV RNA-positive and 5.2% were HPV DNA-positive, and the relative sensitivity was close to 1 for both CIN2+ and CIN3+ outcomes. The relative specificity was 1.005. At 48 months, in the 3226 women who were HPV RNA-negative at baseline, 12 of 2858 (0.4%) had CIN2+; in the 3184 women who were HPV DNA-negative at baseline, 13 of 2821 (0.5%) had CIN2+. There was no difference in the detection of CIN2+ at 48 months between the HPV RNA-negative and HPV DNA-negative women at baseline, and accuracy estimates at 48 months were similar.

Forslund et al. (2019) studied a population-based cohort of 95 023 women in Sweden with available cervical samples collected between May 2007 and January 2012 and frozen at −80 °C. Registry linkages identified that 1204 of these women had CIN3+ after 4 months to 7 years since enrolment. Baseline samples were analysed with an HPV RNA test (Aptima) and an HPV DNA test (cobas 4800), and results from both tests were obtained for 1172 women. Both for women younger than 30 years and for women aged 30 years or older, the HPV RNA and HPV DNA tests had similar sensitivities for the detection of CIN3+. In women aged 30 years or older, the longitudinal sensitivities for CIN3+ occurring during the 2-year period 5–7 years after enrolment were lower for the HPV RNA test, with a relative sensitivity of 0.92 and a relative longitudinal NPV of 1.

Maggino et al. (2016) and Zorzi et al. (2020) published the baseline data and the 5-year follow-up data for two cohorts in two neighbouring areas in Italy, one tested with an HPV RNA test (Aptima) and the other with an HPV DNA test (HC2). Women in both cohorts who tested negative at baseline (22 338 women in the RNA cohort and 68 695 women in the DNA cohort) were followed up. The study reports on the 5-year risk of CIN2+ and CIN3+ and the performance parameters at the 3-year rescreening of a negative HPV RNA test compared with those of a negative HPV DNA test in the two cohorts. The Veneto Cancer Registry was checked to search for invasive cancers and CIN3 diagnosed

up to 5 years after the negative baseline test. The baseline data showed that the proportion of positive Pap tests in HPV-positive women and the cumulative referral rate for colposcopy were both higher (52.8% vs 38.2%, $P < 0.0001$; 4.8% vs 4.5%, $P = 0.04$) in the HPV RNA cohort than in the HPV DNA cohort. The ratio of positive HPV tests, of referral for colposcopy, and of detection of CIN2+ in the RNA cohort compared with the DNA cohort were as follows: HPV prevalence ratio, 1.08 (95% CI, 0.99–1.17); referral ratio, 1.06 (95% CI, 0.95–1.18); and CIN2+ detection ratio, 0.85 (95% CI, 0.54–1.33). The relative 5-year cumulative risks of CIN2+ in the RNA cohort and the DNA cohort were 1.1 and 1.5 per 1000 women, respectively (ratio, 0.74; 95% CI, 0.45–1.16), and the risks of cancer were 4.5 and 8.7 per 100 000 women, respectively (ratio, 0.51; 95% CI, 0.01–4.22). [The study has a major caveat, because the comparison was not performed within the same study population but compared two cohorts in parallel.]

[An important issue relating to HPV RNA tests has been the difficulty of estimating the length of time for which a baseline test has negative predictive value. Given the overall slightly lower sensitivity of the HPV RNA tests, the safety of intervals between screening rounds of longer than 5 years remains uncertain. The studies reporting on longer than 5 years are those of Iftner et al. (2019) and Forslund et al. (2019), who reported on women with negative results at baseline. Although Iftner et al. (2019) did not detect a statistically significant difference between HPV RNA tests and HPV DNA tests, Forslund et al. (2019) found a higher longitudinal sensitivity for the HPV DNA test that was evaluated. The lower sensitivity of HPV RNA tests applied in screening settings may affect the longitudinal NPV at 5 years.]

(b) Use of HPV RNA tests in triage of women with minor abnormal cervical cytology

Ovestad et al. (2011) evaluated two HPV RNA tests – a 5-HPV type RNA test (PreTect HPV-Proofer) and a 14-HPV type RNA test (Aptima) – and two HPV DNA tests – Amplicor and cobas 4800 – for the triage of women with ASC-US or LSIL cytology results. The study included 528 women in Norway selected from a consecutive population-based follow-up of LBC samples for the diagnosis of CIN2/3. [The study has several limitations. One is that the population is a referral population for abnormal results and may not be the most suitable to compare screening tests with a lower HPV viral load. Furthermore, the two RNA tests that were evaluated targeted different sets of HPV types. The 14-HPV type RNA test was significantly more specific than the Amplicor DNA test (ratio, 2.14; 95% CI, 1.23–2.73) and was more sensitive than the 5-HPV type RNA test (ratio, 1.91; 95% CI, 1.43–2.56) but less specific (ratio, 0.47; 95% CI, 0.34–0.63).]

Arbyn et al. (2013b) performed a meta-analysis of studies reporting on an HPV RNA test (Aptima) compared with an HPV DNA test (HC2) for the triage of women with ASC-US or LSIL cytology results. Eight studies were retrieved, which included 1839 ASC-US cases and 1887 LSIL cases. The outcome was histological detection of CIN2+ or CIN3+. All of the women included had undergone a colposcopic evaluation (this may not imply that all of the women had had a biopsy); a negative colposcopy was considered as ascertainment for the absence of disease when no biopsies were taken. Table 4.30 summarizes the relative accuracy of the HPV RNA test compared with the HPV DNA test for CIN2+ or CIN3+ at a threshold of abnormal cytology of ASC-US or LSIL. The sensitivity of the HPV RNA test was not significantly different from that of the HPV DNA test for either of the outcomes measured, but the specificity of the

Table 4.30 Pooled relative sensitivity and specificity of HPV RNA testing compared with HPV DNA testing

Baseline outcome	Outcome after triage	Parameter	Ratio (HPV RNA/HPV DNA) (95% CI)
ASC-US	CIN2+	Sensitivity	1.01 (0.97–1.06)
ASC-US	CIN2+	Specificity	1.19 (1.08–1.31)
ASC-US	CIN3+	Sensitivity	1.01 (0.96–1.06)
ASC-US	CIN3+	Specificity	1.18 (1.08–1.29)
LSIL	CIN2+	Sensitivity	0.96 (0.92–1.03)
LSIL	CIN2+	Specificity	1.37 (1.22–1.54)
LSIL	CIN3+	Sensitivity[a]	0.98 (0.91–1.06)
LSIL	CIN3+	Specificity[a]	1.35 (1.11–1.66)

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion.

[a] The SAS macro MetaDAS failed to converge. Therefore, the pooled relative sensitivity and specificity were computed separately as ratios.
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HPV RNA test was significantly higher both for CIN2+ and for CIN3+. [The study is robust, because the overall analysis was not heterogeneous and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) evaluation did not identify major issues.]

The meta-analysis of Verdoodt et al. (2013) compared the diagnostic accuracy of two HPV RNA tests (PreTect HPV-Proofer and NucliSENS EasyQ), both of which target five HPV types, with that of an HPV DNA test (HC2) for the detection of CIN2+ and CIN3+ in women with ASC-US or LSIL. In women with ASC-US or LSIL, HPV RNA testing was significantly more specific than HPV DNA testing for the detection of CIN2+ (ratio 1.98; 95% CI, 1.7–2.3) or CIN3+ (ratio, 3.36; 95% CI, 2.82–4.0), but was significantly less sensitive for the detection of CIN2+ (ratio, 0.80; 95% CI, 0.73–0.87) and CIN3+ (ratio, 0.74; 95% CI, 0.69–0.80). [The comparison between the HPV RNA tests and the HPV DNA test is expected to be limited because of the difference in the HPV types targeted; the HC2 test targets 13 hrHPV types, whereas both RNA tests that were evaluated target five hrHPV types.]

As a part of the Clinical Evaluation of Aptima mRNA (CLEAR) study, Stoler et al. (2013) evaluated HPV RNA testing for the triage of 939 women with ASC-US cytology for colposcopy referral. A cervical specimen in liquid cytology medium was used to test in a blinded fashion for HPV DNA (cobas 4800), for HPV RNA (Aptima), and for RNA type-specific HPV16, HPV18, and HPV45 for those samples that were HPV RNA-positive. The final diagnoses were based on a consensus panel review of the histology of the biopsy specimen. For detection of CIN2+, the HPV RNA test and the HPV DNA test were equally sensitive (ratio, 1.0; 95% CI, 0.91–1.10), and the HPV RNA test was more specific than the HPV DNA test (ratio, 1.13; 95% CI, 1.04–1.21). Risk stratification using partial HPV genotyping was similar for the two assays. [The CLEAR study had been included in the previous meta-analysis by Gen-Probe (2011), in which data were extracted from a report published by the United States FDA.]

Cook et al. (2017) evaluated an HPV RNA test (Aptima) against an HPV DNA test (HC2) within the HPV FOCAL trial (described above). In addition to the main strategy, further triage strategies to refer women for colposcopy were compared in HPV DNA-positive or HPV RNA-positive women as follows:

Table 4.31 Colposcopy referral rates and CIN2+ and CIN3+ detection rates by baseline and triage strategies

Primary test result	Triage strategy result	Number of women screened	Colposcopy referral rate (%) (95% CI)	Detection rate (per 1000 women screened) (95% CI)	
				CIN2+	CIN3+
Baseline HPV DNA+	ASC-US+	125	36.0 (30.3–42.7)	11.2 (8.2–15.3)	4.0 (2.4–6.8)
Baseline HPV DNA+	Persistent HPV DNA+ and/or ASC-US+	86	24.8 (20.1–30.5)	3.2 (1.8–5.7)	1.2 (0.4–3.0)
Baseline HPV RNA+	ASC-US+	107	30.8 (25.6–37.1)	10.9 (8.0–15.0)	4.0 (2.4–6.8)
Baseline HPV RNA+	HPV16/18/45+	67	19.3 (15.2–24.4)	7.8 (5.4–11.3)	3.5 (2.0–6.0)
Baseline HPV RNA+	ASC-US+, or NILM and HPV16/18/45+	133	38.3 (32.4–45.2)	12.4 (9.2–16.6)	4.6 (2.8–7.5)

ASC-US, atypical squamous cells of undetermined significance; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; NILM, negative for intraepithelial lesion or malignancy.

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(i) HPV DNA-positive and ASC-US+, (ii) HPV DNA-positive with 12-month HPV persistence and/or ASC-US+, (iii) HPV RNA-positive and ASC-US+, (iv) HPV RNA-positive and HPV16/18/45-positive, and (v) HPV RNA-positive and ASC-US+, or HPV RNA-positive and NILM and HPV16/18/45-positive. [Genotyping was performed with an HPV RNA (Aptima) HPV16/18/45 genotyping assay.] Table 4.31 shows the accuracy results of the different triage strategies. [The Working Group noted that women who were HPV DNA-negative but HPV RNA-positive were not referred for colposcopy; this could lead to an underestimate of an added value of the HPV RNA test, although this should be minimal, given the slightly lower sensitivity of HPV RNA tests compared with HPV DNA tests.] Compared with the triage strategy of immediate referral for colposcopy of women who were HPV DNA-positive with abnormal cytology at baseline and those with 12-month HPV persistence (60.8 per 1000 women screened), the colposcopy referral rate was significantly lower (38.3 per 1000 women screened; *P* < 0.001) in the strategy in which HPV RNA-positive women with abnormal LBC or HPV16/18/45 positivity were referred at baseline.

4.4.7 Triage of women with a positive primary HPV screening test result

Testing for the presence of HPV (in the absence of triage) is inherently limited in terms of its specificity for the presence of histologically confirmed CIN2+ and CIN3+ (Arbyn et al., 2012). Although hrHPV positivity predicts an increased risk of the future development of CIN2+ and CIN3+ (even if disease is not present at the time of the index screening test) (Katki et al., 2011), the lower cross-sectional specificity nevertheless implies that some screen-positive women might be followed up unnecessarily. Therefore, appropriate triage testing, management, and follow-up of HPV-positive women is of critical importance to optimize the balance of benefits and harms of primary HPV screening. The general principle is to refer for diagnostic workup women who are at a higher risk of having a current or incipient precancer, to return to routine screening women who are at low risk, and to keep under surveillance women who are at intermediate risk (Arbyn et al., 2017).

(a) Methods

For this *Handbook*, the Working Group updated a previous meta-analysis on the accuracy of six tests or combinations of tests used to triage hrHPV-positive women identified at screening for the detection of underlying cervical precancer ([HAS, 2019](#)). Literature retrieval was extended up to 31 January 2020. The Working Group drafted the review question in PICOS form (population, intervention, comparator, outcome, and studies) to determine the inclusion and exclusion criteria for the studies. PICOS components of the research question are summarized in Box S1 (Annex 1; web only; available from https://publications.iarc.fr/604). Studies were eligible if (i) cross-sectional and/or longitudinal outcome data were available for women with a positive hrHPV screening test result triaged with an index test, and (ii) verification with the reference standard (colposcopy and targeted biopsy, possibly complemented with random biopsies and/or endocervical curettage) was performed on all women or on women with at least one positive triage test result. Normal satisfactory colposcopy without biopsy was accepted as ascertainment of the absence of CIN2+. The methodological quality of the selected studies was assessed using the QUADAS-2 checklist ([Whiting et al., 2011](#)).

The current review was limited to one-time (reflex) triage strategies for women with a positive hrHPV test result on a clinician-collected cervical specimen using the following tests: (i) cytology at a threshold of ASC-US+, (ii) genotyping for HPV16/18, (iii) p16/Ki-67 immunocytochemistry (dual staining), (iv) VIA, (v) the combination of HPV16/18 genotyping and cytology, and (vi) the combination of HPV16/18 genotyping and VIA. Strategies involving other triage tests or combinations and two-time triage strategies (including surveillance of women who were reflex triage-negative) and triage of women with an HPV-positive self-collected sample are not included here.

The numbers of true positives and false positives and true negatives and false negatives were extracted from each primary study to compute the sensitivity, specificity, PPV, NPV, the complement of NPV (i.e. 1 − NPV [cNPV]), the test positivity rate, and the underlying prevalence of CIN2+ and CIN3+. Standard statistical procedures for pooling diagnostic accuracy data were used ([Leeflang et al., 2008](#)). The results were displayed graphically in forest plots and summary ROC (sROC) curves. For each triage approach, the relative sensitivity and specificity compared with reflex cytology at a threshold of ASC-US+ was also assessed. Finally, to illustrate the principle of triage as it applies in a specific local setting, the implied performance of CIN3+ risk-based stratification was considered for each triage approach, given examples of potentially acceptable local risk thresholds for either return to routine screening or referral for colposcopy. The numbers of false-positive and true-positive and false-negative and true-negative results were calculated for a population of 1000 triaged hrHPV-positive women, as were the PPV and cNPV for CIN3+. In addition, the proportion of triage-positive women who would be referred for colposcopy was calculated, together with the number of women who must be referred for colposcopy to detect one case of CIN3+ (= 1/PPV). For this exercise, three background situations were simulated in terms of the underlying risk of CIN3+: (i) a low-risk situation, with a prevalence of CIN3+ of 5% (corresponding to the 10th percentile of the distribution of observed prevalence throughout the meta-analysis); (ii) an intermediate-risk situation, with a prevalence of CIN3+ of 8% (corresponding to the median prevalence); and (iii) a high-risk situation, with a prevalence of CIN3+ of 17% (corresponding to the 90th percentile of the distribution of observed prevalence throughout the meta-analysis).

(b) Results

Overall, 93 studies were included in the meta-analysis; the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is shown in Fig. S1 (Annex 1; web only; available from https://publications.iarc.fr/604). Most QUADAS-2 items for the included studies were assessed as satisfactory or borderline; see Fig. S2 (Annex 1; web only; available from https://publications.iarc.fr/604). The summary results of all the meta-analyses are presented in Table 4.31. The detailed results are presented in Figs. S3–S5, and Table S1 (Annex 1; web only; available from https://publications.iarc.fr/604).

(i) Triage with cytology at a threshold of ASC-US+

The pooled sensitivity for CIN2+ in 39 studies was 72% (95% CI, 65–77%) and for CIN3+ in 28 studies was 78% (95% CI, 69–84%), and the pooled specificity for < CIN2 was 75% (95% CI, 69–80%) (see Fig. 4.5, Fig. S3 [Annex 1; web only; available from https://publications.iarc.fr/604], Table 4.32). The pooled relative sensitivity for the detection of CIN2+ was higher (ratio, 1.22; 95% CI, 1.04–1.44) and the specificity was lower (ratio, 0.75; 95% CI, 0.64–0.88) in the group of studies in which the cytologists were aware of the HPV status compared with the group of studies in which the cytologists were blinded to the HPV status; for the sROC curves stratified by the cytologists' knowledge of the HPV status, see Fig. S4B (Annex 1; web only; available from https://publications.iarc.fr/604). For the detection of CIN3+, the impact of the cytologists' knowledge of the HPV status was smaller (detailed results not shown). There were no significant differences in accuracy for detection of CIN2+ or CIN3+ between conventional cytology and LBC methods used in triage of HPV-positive women when ASC-US+ was used as the threshold (detailed results not shown). However, the accuracy of cytology at a threshold of ASC-US+ for CIN2+ was higher in HPV16/18-positive women than in HPV16/18-negative women (detailed results not shown).

(ii) Triage with VIA

Fig. 4.6 shows a forest plot for the meta-analysis of the absolute sensitivity and specificity of triage of hrHPV-positive women with VIA for the detection of CIN3+. The sensitivity was extremely heterogeneous between studies, varying from 6% (Asthana & Labani, 2015) to 100% (Almonte et al., 2020) for CIN2+ and from 7% to 100% for CIN3+ (Fig. 4.6). Exclusion of these two extreme observations yielded a pooled sensitivity of 64% (95% CI, 56–72%) for CIN2+ and of 69% (95% CI, 61–75%) for CIN3+, and a pooled specificity for < CIN2 of 79% (95% CI, 73–84%) (Table 4.32). The relative accuracy estimates (VIA compared with cytology) did not differ from unity; the sensitivity ratio was 1.15 (95% CI, 0.76–1.83) for CIN2+ and 1.01 (95% CI, 0.70–1.45) for CIN3+, and the specificity ratio for < CIN2 was 0.82 (95% CI, 0.58–1.16) (detailed results not shown). Very wide interstudy variation in the relative sensitivity and specificity was observed ($I^2 > 97\%$; data not shown).

(iii) Triage with HPV16/18 genotyping

The pooled sensitivity of HPV16/18 genotyping to triage hrHPV-positive women was 53% (95% CI, 50–56%) for CIN2+ and 61% (95% CI, 57–65%) for CIN3+, and the pooled specificity for < CIN2 was 75% (95% CI, 70–79%) (Table 4.32, Fig. S4 and Fig. S5 [Annex 1; web only; available from https://publications.iarc.fr/604]). For the detection of CIN2+, HPV16/18 genotyping was less sensitive (ratio, 0.85; 95% CI, 0.75–0.96) but similarly specific (ratio, 1.03; 95% CI, 0.95–1.12) compared with cytology at a threshold of ASC-US+. For the detection of CIN3+, there was no significant difference in accuracy between triage with HPV16/18 genotyping and reflex cytology at a threshold of ASC-US+.

Fig. 4.5 Meta-analysis of the absolute sensitivity and specificity of triage of hrHPV-positive women with reflex cytology at a threshold of ASC-US+ for the detection of CIN3+

Study	Sensitivity (95% CI)	Specificity (95% CI)
Kulasingam et al. (2002)	0.753 (0.642, 0.844)	0.477 (0.431, 0.524)
Ronco et al. (2006b)	0.827 (0.697, 0.918)	0.678 (0.654, 0.700)
Naucler et al. (2009)	0.729 (0.582, 0.847)	0.857 (0.805, 0.900)
Castle et al. (2011)	0.528 (0.464, 0.591)	0.752 (0.736, 0.768)
Rijkaart et al. (2012c)	0.832 (0.761, 0.889)	0.758 (0.724, 0.790)
Bian et al. (2013)	0.900 (0.555, 0.997)	0.755 (0.660, 0.835)
Ferreccio et al. (2013)	0.404 (0.270, 0.549)	0.915 (0.894, 0.934)
Leinonen et al. (2013)	0.952 (0.867, 0.990)	0.629 (0.610, 0.648)
Muwonge et al. (2014)	0.878 (0.819, 0.923)	0.655 (0.635, 0.674)
Pan et al. (2014)	0.955 (0.931, 0.972)	0.501 (0.486, 0.517)
Tian et al. (2014)	0.698 (0.632, 0.758)	0.700 (0.667, 0.731)
Asthana & Labani (2015)	0.636 (0.308, 0.891)	0.857 (0.784, 0.913)
Rebolj et al. (2015)	0.571 (0.410, 0.723)	0.699 (0.627, 0.765)
Terrazas et al. (2015)	0.404 (0.270, 0.549)	0.915 (0.894, 0.934)
Wentzensen et al. (2015)	0.838 (0.751, 0.905)	0.487 (0.461, 0.514)
Gustinucci et al. (2016)	0.741 (0.537, 0.889)	0.934 (0.904, 0.957)
Zhao et al. (2016a, b)	0.955 (0.933, 0.972)	0.498 (0.483, 0.512)
Agorastos et al. (2017)	0.667 (0.349, 0.901)	0.833 (0.779, 0.879)
Cook et al. (2017)	0.778 (0.524, 0.936)	0.587 (0.526, 0.647)
Isidean et al. (2017)	0.600 (0.433, 0.751)	0.837 (0.802, 0.868)
Kocsis et al. (2017)	0.421 (0.309, 0.540)	0.778 (0.753, 0.801)
Passamonti et al. (2017)	1.000 (0.872, 1.000)	0.641 (0.585, 0.695)
Sangrajrang et al. (2017)	0.714 (0.419, 0.916)	0.580 (0.498, 0.658)
Tshomo et al. (2017)	0.722 (0.465, 0.903)	0.848 (0.764, 0.910)
Wu et al. (2017)	0.797 (0.692, 0.880)	0.741 (0.712, 0.769)
Rezhake et al. (2018)	1.000 (0.692, 1.000)	0.510 (0.446, 0.574)
Luo et al. (2019)	0.891 (0.827, 0.938)	0.572 (0.541, 0.602)
Torres-Ibarra et al. (2019)	0.440 (0.332, 0.553)	0.734 (0.706, 0.760)
Overall	0.775 (0.694, 0.839)	0.727 (0.667, 0.779)

ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; hrHPV, high-risk human papillomavirus.
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(iv) Triage with immunocytochemistry (dual staining) for p16/Ki-67

Dual staining for p16/Ki-67 was more sensitive than reflex cytology at a threshold of ASC-US+, but the difference was significant only for CIN2+ (81% vs 72%; ratio, 1.12; 95% CI, 1.01–1.25) and not for CIN3+ (Table 4.32, Fig. S4 and Fig. S5 [Annex 1; web only; available from https://publications.iarc.fr/604]). The specificity of dual staining for < CIN2 was similar to that of cytology at a threshold of ASC-US+ (69% vs 75%).

(v) Triage with HPV16/18 genotyping combined with cytology or VIA

HPV16/18 genotyping is usually not used as a stand-alone method to triage hrHPV-positive women. A combined strategy in which HPV16/18-positive women are directly referred for colposcopy and women who are positive only for other carcinogenic HPV types are further triaged with cytology, with referral for colposcopy when cytology shows ASC-US+, had a sensitivity of 83% (95% CI, 79–86%) for CIN2+ and 86% (95% CI, 72–84%) for CIN3+, and the specificity

Fig. 4.6 Meta-analysis of the absolute sensitivity and specificity of triage of hrHPV-positive women with VIA for the detection of CIN3+

Study	Sensitivity (95% CI)	Specificity (95% CI)
SPOCCS-1 (2001)	0.786 (0.632, 0.897)	0.639 (0.583, 0.691)
ACCP (2008) [Mumbai (India)]	0.543 (0.366, 0.712)	0.828 (0.774, 0.874)
ACCP (2008) [Kolkata-2 (India)]	0.680 (0.465, 0.851)	0.865 (0.826, 0.898)
ACCP (2008) [Trivandrum-2 (India)]	0.868 (0.719, 0.956)	0.721 (0.663, 0.774)
ACCP (2008) [Kolkata-1 (India)]	0.632 (0.384, 0.837)	0.788 (0.738, 0.833)
Muwonge et al. (2014)	0.808 (0.741, 0.864)	0.618 (0.598, 0.638)
Qiao et al. (2014)	0.531 (0.427, 0.634)	0.852 (0.828, 0.874)
Basu et al. (2015)	0.684 (0.604, 0.757)	0.861 (0.840, 0.879)
Mittal et al. (2016)	0.663 (0.587, 0.733)	0.838 (0.815, 0.860)
Zhao et al. (2016a, b)	0.544 (0.497, 0.589)	0.842 (0.831, 0.852)
Wang et al. (2017)	0.600 (0.361, 0.809)	0.909 (0.871, 0.939)
ESTAMPA (2020) [Paraguay]	0.609 (0.385, 0.803)	0.782 (0.713, 0.842)
ESTAMPA (2020) [Peru]	0.500 (0.118, 0.882)	0.754 (0.627, 0.855)
ESTAMPA (2020) [Colombia]	0.906 (0.833, 0.954)	0.438 (0.410, 0.467)
ESTAMPA (2020) [Bolivia]	0.500 (0.068, 0.932)	0.778 (0.577, 0.914)
Overall	0.688 (0.613, 0.754)	0.786 (0.725, 0.836)

Sensitivity (95% CI) — Specificity (95% CI)

ACCP, Alliance for Cervical Cancer Prevention; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; hrHPV, high-risk human papillomavirus; SPOCCS, Shanxi Province Cervical Cancer Screening Study; VIA, visual inspection with acetic acid.
ACCP (2008): main reference is Arbyn et al. (2008); ESTAMPA (2020): main reference is Almonte et al. (2020); SPOCCS-1 (2001): main reference is Belinson et al. (2001).
Note: Unpublished data were provided by IARC from the ESTAMPA study (Almonte et al., 2020).
Created by the Working Group.

for < CIN2 was 55% (95% CI, 48–62%). Only two studies provided data for the combination of HPV16/18 genotyping and VIA (Table 4.32, Fig. S4 and Fig. S5; Annex 1; web only; available from https://publications.iarc.fr/604).

(vi)   Utility of triage based on the post-test risk of CIN3+

Fig. 4.7 is an example pre-test–post-test probability plot showing the risk of CIN3+ through the triage pathway applied to hrHPV-positive women starting with partial genotyping (i.e.

HPV16/18-positive). Women who are positive only for other hrHPV types receive a secondary triage with cytology at a threshold of ASC-US+. In Fig. 4.7, a median underlying risk (8%) of CIN3+ in hrHPV-positive women (notionally representing, for example, a population in a middle-income or high-income country) is assumed. Triage with HPV16/18 genotyping enables post-test separation of the population of women into those who are positive for HPV16/18, with a higher risk (almost 20%) of CIN3+, and those who are negative for HPV16/18, with a

Table 4.32 Pooled cross-sectional sensitivity and specificity of selected tests used to triage hrHPV-positive women to detect CIN2+ or CIN3+

Triage test	Outcome	Number of studies	Referral rate (%) (IQR or range)[a]	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
ASC-US cytology (all)	CIN2+	39	33.8 (28.9–43.8)[a]	71.5 (65.2–77.1)	74.7 (69.2–79.5)
VIA	CIN2+	17	22.4 (19.3–35.3)[a]	64.2 (56.1–71.5)	79.2 (73.0–84.2)
HPV16/18 genotyping	CIN2+	16	30.7 (20.2–34.3)[a]	52.9 (50.2–55.7)	74.9 (70.3–79.0)
p16/Ki-67 dual staining	CIN2+	5	36.5 (29.4–46.0)	80.8 (74.5–85.8)	69.0 (61.1–75.9)
HPV16/18 genotyping, ASC-US+ cytology if positive for other hrHPV types	CIN2+	12	53.5 (44.6–68.8)[a]	82.6 (79.2–85.5)	55.4 (48.2–62.4)
HPV16/18 genotyping, VIA if positive for other hrHPV types	CIN2+	2	45.3 (43.3–49.4)	87.2 (78.4–92.8)	59.9 (56.2–63.4)
ASC-US cytology (all)	CIN3+	28	[b]	77.5 (69.4–83.9)	72.7 (66.7–77.9)
VIA	CIN3+	15	[b]	68.8 (61.3–75.4)	78.6 (72.5–83.6)
HPV16/18 genotyping	CIN3+	10	[b]	61.2 (57.2–65.2)	74.9 (68.7–80.2)
p16/Ki-67 dual staining	CIN3+	4	[b]	85.1 (77.4–90.5)	63.8 (55.6–71.2)
HPV16/18 genotyping, ASC-US+ cytology if positive for other hrHPV types	CIN3+	9	[b]	85.8 (72.1–84.2)	67.5 (60.1–72.4)
HPV16/18 genotyping, VIA if positive for other hrHPV types	CIN3+	2	[b]	91.5 (79.4–96.8)	57.6 (54.0–61.0)

ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; IQR, interquartile range; VIA, visual inspection with acetic acid.

[a] Referral rate is the percentage of hrHPV-positive women with a positive triage test result. IQR if ≥ 8 studies; range if < 8 studies.

[b] Referral rate is not given for the CIN3+ outcome, because it should be the same as for the CIN2+ outcome.

lower risk (about 3%). This latter group can be further triaged with cytology to resolve their risks of CIN3+ to 6.5% (ASC-US+ cytology) and < 2% (cytology-negative). [The triage process can effectively risk-stratify women for the presence of underlying CIN3+. This example effectively illustrates context sensitivity and how the risk stratification inherent in the triage process must ultimately consider the underlying burden of disease as well as the local acceptability of various levels of risk.]

Table S1 (Annex 1; web only; available from https://publications.iarc.fr/604) shows the post-test risks of CIN3+ in triage-positive women (PPV) and in triage-negative women (cNPV) for all six triage strategies in low-risk, intermediate-risk, and high-risk situations. The green shading indicates, as an example, the decision thresholds chosen for risk of CIN3+ at > 10% for

referral and < 1% for return to routine screening. [It should be noted that each local programme should choose its own decision thresholds in the context of locally acceptable risks. More complex algorithms than those assessed here can be considered to fine-tune management, particularly in relation to the management of an intermediate-risk group who are hrHPV-positive but have a negative triage test result at the index test, for whom surveillance (i.e. two-time triage testing) is an option (Arbyn et al., 2020).]

4.4.8 Harms of HPV testing

The harms of HPV testing consist of the psychosocial impact of screening and of a positive HPV test result, and the physical and psychosocial harms of the sampling procedure and of diagnostic follow-up procedures and

Fig. 4.7 Pre-test–post-test probability plot, showing the risk of CIN3+ through the triage pathway applied to hrHPV-positive women, computed from pooled accuracy estimates applied in a given pre-test risk situation
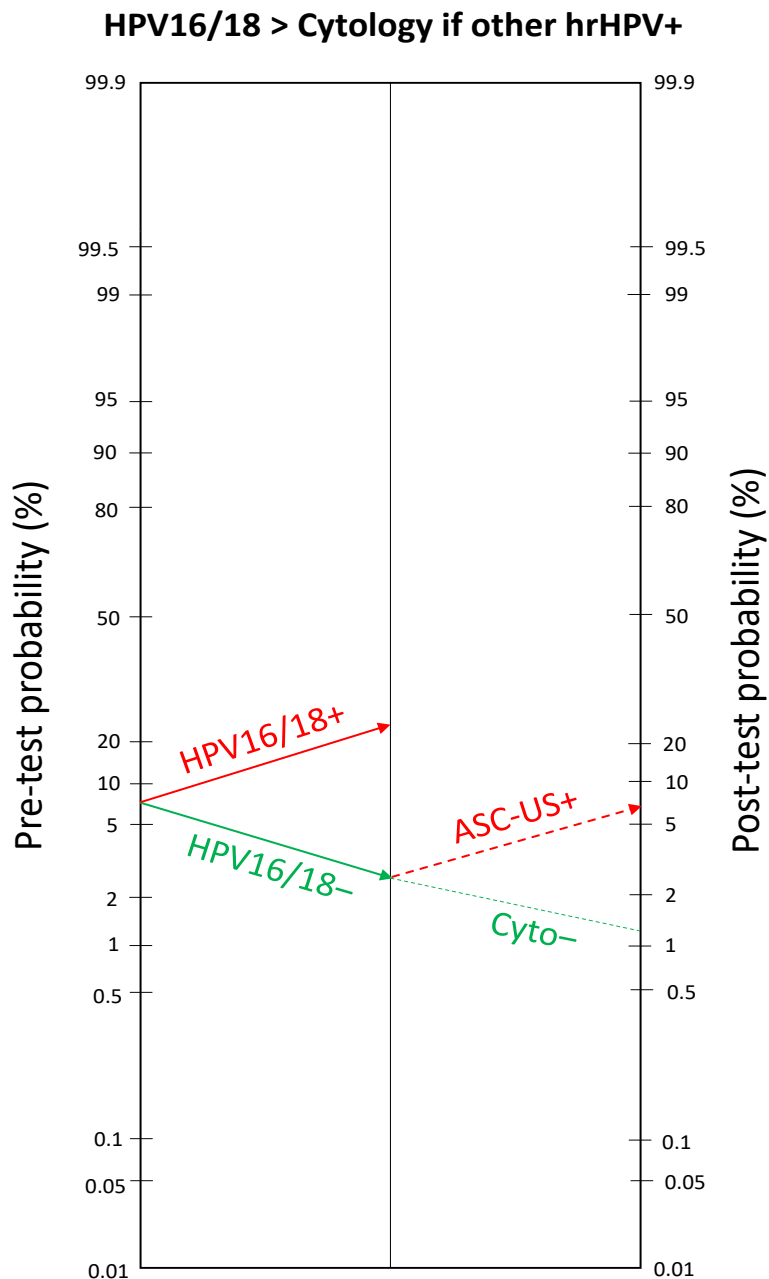
Triage with HPV16/18 genotyping followed by colposcopy if HPV16/18-positive. Women who are positive only for other hrHPV types are further triaged with cytology and referred for colposcopy if ASC-US+.

The first triage is applied to a median-risk situation with a pre-test risk of 8% (see left vertical axis). Applying HPV16/18 genotyping stratifies the risk to 19.5% if HPV16/18-positive and to 2.8% if positive only for other hrHPV types. Applying cytology to women who are positive only for other hrHPV types stratifies the risk to 6.5% if ASC-US+ and to 1.3% if cytology is normal.

ASC-US+, atypical squamous cells of undetermined significance or worse; CI, confidence interval; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; Cyto, cytology; hrHPV, high-risk human papillomavirus; VIA, visual inspection with acetic acid.
Created by the Working Group.

treatments. The psychosocial impact of a positive HPV test result is potentially greater than that of an abnormal cytology result, because HPV is sexually transmitted. Qualitative information about psychosocial harms collected by focus groups and in-depth interviews (Anhang et al., 2004; Kahn et al., 2005; McCaffery et al., 2006; Waller et al., 2007; Daley et al., 2010; O'Connor et al., 2014; Patel et al., 2018) has revealed that a positive HPV test result may cause anxiety and distress and may lead to concerns about the association between HPV and cervical cancer. It may also evoke feelings of stigma and shame and influence sexual relationships by leading to feelings of blame or guilt towards previous or current sexual partners.

The psychosocial impact of HPV testing in cervical screening programmes has been estimated by questionnaire surveys. These include studies that measured harms of HPV testing as a primary screening test (McCaffery et al., 2004; Kitchener et al., 2008; Hsu et al., 2018; Andreassen et al., 2019; McBride et al., 2020) and studies that measured harms of HPV testing in women with ASC-US (Maissi et al., 2004; McCaffery et al., 2010; Kwan et al., 2011; Wang et al., 2011; Garcés-Palacio et al., 2018). To understand what type of information should be included in HPV screening invitation letters, in leaflets, and on websites in order to minimize psychosocial harms, several studies have examined whether the psychological harms experienced are influenced by a woman's knowledge about HPV (Waller et al., 2007; Papa et al., 2009; Burger et al., 2014; Markovic-Denic et al., 2018; Patel et al., 2018).

The harms associated with collection of samples may be different for clinician collection and sample collection at home using a self-sampling device. The experience with self-sampling has been assessed in questionnaire surveys (Nelson et al., 2017) containing items on the preference for self-sampling compared with clinician collection, and sometimes also items on the physical and/or psychosocial harms of the collection procedure.

Finally, the magnitude of the harms of HPV testing, diagnostic workup, and treatment of high-grade lesions in cervical screening can be represented by the numbers of screen-positive women, referrals for colposcopy, and treatments, and may be higher for HPV-based screening than for VIA or cytology-based screening because of the relatively high HPV test positivity rate in screening (Arbyn et al., 2012). The proportions of screen-positive women, referrals for colposcopy, and treatments have been reported in meta-analyses of diagnostic HPV screening studies, RCTs, and implementation studies of HPV screening. The magnitude of diagnostic and treatment harms of HPV DNA-based programmes compared with cytology-based and VIA-based programmes was presented in Sections 4.4.2 and 4.4.3, respectively.

(a) Psychosocial harms of HPV testing as a primary screening test

The first study on the psychosocial impact of HPV testing as a primary test in cervical screening was conducted in the United Kingdom in 271 women (mean age, 32 years) who received HPV testing and cytology testing (McCaffery et al., 2004). Anxiety was measured by the short form of the STAI-6 (Marteau & Bekker, 1992) and distress by the Cervical Screening Questionnaire (CSQ; Wardle et al., 1995), and results were collected within 1 month. Among women with normal cytology, anxiety and distress were higher in HPV-positive women than in HPV-negative women. A similar pattern was observed in women with abnormal or unsatisfactory cytology, but the variability of the estimates was high because the stratum size was only 40 women. In addition, more HPV-positive women than HPV-negative women felt worse about their current partner and about previous and future partners, and this effect was similar for women

with normal cytology and those with abnormal or unsatisfactory cytology.

Psychosocial outcomes in women with normal cytology were also measured in a substudy of the ARTISTIC trial (Kitchener et al., 2008, 2009a), a population-based randomized screening trial in the United Kingdom. Women with normal or mildly abnormal cytology recruited in the ARTISTIC trial were randomized either to cytology with revealed HPV testing or to cytology with concealed HPV testing. The women in the HPV-revealed arm received the results of their HPV test with their baseline cytology result; the women in the HPV-concealed arm were informed of only the cytology result. Anxiety, distress, and sexual satisfaction were assessed in 705 participants after about 2 weeks. Anxiety was measured by the STAI-6, distress was measured by the GHQ (Bridges & Goldberg, 1986), and sexual satisfaction was measured by the Sexual Rating Scale (Garratt et al., 1995). When the analysis was restricted to women who were aware of the HPV test result (the revealed arm) and who were cytology-negative, higher levels of anxiety and distress were reported in women who were HPV-positive than in women who were HPV-negative (41% vs 29%; OR, 1.70; 95% CI, 1.33–2.17). However, there was no evidence of a higher level of anxiety or distress in the revealed arm compared with the concealed arm (OR, 0.99; 95% CI, 0.81–1.21). A significant 7% difference on the Sexual Rating Scale was observed in HPV-positive women with normal cytology compared with the group of women with normal cytology and no revealed HPV test result.

A randomized implementation study of primary HPV screening versus cytology screening in Norway measured anxiety and depression by means of the Patient Health Questionnaire-4 (PHQ-4) (Kroenke et al., 2009) in 1007 screened women (Andreassen et al., 2019) randomized to either HPV testing every 5 years (followed by cytology if HPV-positive) or cytology testing every 3 years (followed by HPV testing if low-grade cytology was detected). Compared with women who were screened with cytology, women screened with an HPV test were not more likely to have mild, moderate, or severe anxiety and depression scores. Moreover, no differences in mean anxiety and depression levels were found when comparing HPV-positive women with normal cytology from the HPV screening group with women with normal cytology from the cytology group. [A possible explanation for the absence of an effect on psychosocial outcomes in the study in Norway is that women answered the questionnaire 4 months to 2 years after having received their last screening result, and elevations in anxiety and depression levels may have been temporary and levels may already have returned to normal. There was also considerable variation among participants in anxiety and depression levels, with some participants showing moderate or severe anxiety and depression levels.]

An inventory of the psychosocial harms in primary HPV screening implemented in a middle-income setting was conducted by Arrossi et al. (2020). In 163 HPV-positive women participating in the regional primary HPV screening programme in Jujuy, Argentina, psychosocial impact was measured by means of the Psycho-Estampa Scale, which was designed and validated for use in Latin American women. The Psycho-Estampa Scale consists of five domains: (i) an emotional domain, related to feelings about having a sexually transmitted infection; (ii) a sexuality domain, related to attitude and practice in sexual relationships; (iii) an uncertainty of information domain; (iv) a domain pertaining to the impact on family members; and (v) a worries domain, covering worries about HPV, cancer, and treatment. In the study population, the mean levels were highest for worries about HPV, cancer, and treatment but were also elevated for the other domains. The scores were higher in women with abnormal cytology triage than in women with normal cytology.

A systematic review of 25 studies on the effect of a positive HPV test on psychosexual outcomes (Bennett et al., 2019) considered overall psychosexual impact, sexual satisfaction and pleasure, frequency of sex, interest in sex, and feelings about partners and relationships. The studies included were very heterogeneous, which made it difficult to draw conclusions about the psychosexual impact of HPV testing, but in general women were concerned about transmitting HPV to a partner and about where the infection came from.

The longitudinal pattern of psychosocial outcomes was studied in England in a questionnaire survey in 1127 women aged 24–65 years who were screened at one of the primary HPV screening pilot centres; the study included a control group with negative cytology who were not tested for HPV (McBride et al., 2020). Elevated anxiety (STAI-6) and distress (GHQ) scores were recorded in HPV-positive women compared with women with negative cytology in the first 3 months after the test result had been received. However, after 12 months, anxiety and distress levels had returned to normal levels, irrespective of the HPV test result at 12 months. With respect to disease-related concerns, a positive HPV test result at baseline and at 12 months contributed to worry about cancer, and HPV clearance at 12 months contributed to reassurance. [The observation that a positive HPV test result at 12 months did not lead to an increase in the mean levels of anxiety and distress but was associated with worry about cancer suggests that although a positive HPV test result gives rise to disease-related concern initially, it is not disruptive of daily functioning when repeated.]

The observation that distress levels decrease over time was confirmed in a smaller study of 70 HPV-positive women in Taiwan, China, who were followed up until 12 months after a positive HPV test result (Hsu et al., 2018).

(b) Psychosocial harms of HPV testing as triage after an abnormal cytology result

One of the first studies that evaluated the psychosocial harms of HPV testing in women with an abnormal cytology result was a pilot study embedded in routine cytology screening in England, which recruited 1376 women with a normal or BMD cytology result (ASC-US/LSIL); 867 of the women with ASC-US/LSIL also had an HPV test (Maissi et al., 2004). The 536 women with a positive HPV test result were compared with the 331 women with a negative HPV test result and the 509 women who were not tested for HPV. Women with a positive HPV test result had the highest level of anxiety as measured by the STAI-6, the highest level of distress as measured by the GHQ, and the largest concern about the test result compared with the other groups. Women with an abnormal cytology result, whether tested for HPV or not, were less likely to know what their results meant compared with women with a normal cytology result; 26% of women with a positive HPV test result stated that they did not know what this meant for their health. Levels of anxiety, distress, and concern were similar in women with a negative HPV test result and in women who were not tested for HPV. [Because the study was cross-sectional, it did not provide information about the duration of elevated levels of anxiety and distress.] After a 6-month follow-up assessment (Maissi et al., 2005), mean levels of anxiety and distress were lower and did not differ between the three groups. The level of concern about a positive HPV test result was still elevated after 6 months compared with the level of concern after a negative HPV test result or no HPV test, but the level of concern had decreased from the baseline level. Worries about sexual health were measured for the first time after 6 months, and they were also higher in the group with a positive HPV test result.

An association between psychosocial harms and HPV testing does not necessarily imply that HPV triage has a negative effect on psychosocial outcomes in women with ASC-US. For example (as mentioned above) in the ARTISTIC trial, HPV-positive and HPV-negative women had different levels of psychosocial outcomes, but there were no significant differences in mean levels between the cytology and HPV randomization arms. To address this for women with ASC-US, in a pragmatic, randomized screening study in Australia of 314 women with an ASC-US test result, women were randomized to HPV testing, repeat cytology testing after 6 months, or an informed choice of either test supported by a decision tool (McCaffery et al., 2010). In the informed-choice arm, 61 (64%) women chose HPV testing and 35 (36%) chose repeat cytology testing. Psychosocial outcomes were measured after 2 weeks and after 3, 6, and 12 months. After 2 weeks, no mean effect of HPV testing was observed on anxiety as measured by the STAI-6 or on distress as measured by the CSQ (Wardle et al., 1995), although HPV testing was associated with 57% of women having intrusive thoughts in the HPV testing arm, compared with 32% in the repeat cytology testing arm and 43% in the informed-choice arm. However, after 1 year, most of the women in the HPV testing arm did not report residual intrusive thoughts, and distress was highest in the repeat cytology testing arm.

The temporary nature of anxiety, as observed in the studies in England and Australia described above, was confirmed in a study of 299 ethnic Chinese women in Hong Kong SAR with an ASC-US test result who received adjunct HPV testing (Kwan et al., 2011). Baseline differences in the mean level of anxiety (STAI-6) between HPV-negative and HPV-positive women had disappeared after 6 months. The effect of HPV testing on the HPV Impact Profile (HIP) was also examined. The HIP scale is a combined, multi-dimensional scale (Mast et al., 2009) with seven dimensions: worries and concerns, emotional impact, sexual impact, self-image, partner issues and transmission, interactions with physicians, and health control and impact on daily living. HIP scores were different for HPV-positive and HPV-negative women at baseline and at 6 months, although the differences were smaller at 6 months.

A hospital-based survey in China in 2605 women who had visited the hospital in the previous 3 months (Wang et al., 2011) confirmed that HIP scores were elevated in women with an HPV-positive ASC-US test result compared with women with an HPV-negative ASC-US test result or women with normal cytology. A pragmatic trial in Colombia compared psychosocial outcomes in 675 women (Garcés-Palacio et al., 2020) randomized to repeat cytology testing, HPV testing, or colposcopy after an ASC-US test result. The study found that anxiety measured by a long-form 20-item version of the Spielberger anxiety scale (STAI-20) and the HIP was higher in HPV-positive women than in HPV-negative women at 2 months, but that the differences in mean levels had disappeared after 1 year. There were no significant differences between the different randomization groups.

A strength of the randomized trials in Australia (McCaffery et al., 2010) and Colombia (Garcés-Palacio et al., 2020) is that the direct causal effect of HPV testing on psychosocial harms in the screening population is measured. This causal effect of learning about the HPV test result on psychosocial outcomes cannot be concluded from a comparison of psychosocial outcomes in HPV-positive and HPV-negative women, because HPV-positive women may have different levels of harms than HPV-negative women before the HPV test result is revealed. This conjecture was examined by a study in 2842 women in the United Kingdom (Johnson et al., 2011) participating in the TOMBOLA trial (Cotton et al., 2006). Psychosocial outcomes were measured before the HPV test result was

revealed. Anxiety was measured by the HADS (Zigmond & Snaith, 1983). In White women, there were no baseline differences in anxiety and cancer worries, but in non-White women, anxiety was lower in HPV-positive women than in HPV-negative women. In non-smokers, cancer worry was more common in HPV-positive women than in HPV-negative women; the opposite association was observed in ex-smokers.

[This suggests that the effect on psychosocial outcomes of knowing the HPV test result may be somewhat confounded by baseline differences between HPV-positive and HPV-negative women.]

(c) Psychosocial harms and knowledge about HPV

Mass education about HPV can prevent anxiety and psychological distress associated with HPV testing (Anhang et al., 2004). Focus group interviews (Anhang et al., 2005) identified that women desire detailed information about HPV, including susceptibility, risk of cervical cancer, and the effect of preventive interventions on this risk. The studies described here aimed to estimate the association between knowledge of HPV and psychosocial harms.

Waller et al. (2007) conducted a web-based survey in the United Kingdom in 811 female students. The participants were asked to imagine that they had had a positive HPV test result, and the study assessed the impact of their knowledge that HPV is sexually transmitted and about the high prevalence of HPV infection on stigma, shame, and anxiety by withholding pieces of information from some participants. Knowledge of the high prevalence was associated with lower levels of stigma, shame, and anxiety, whereas knowledge that HPV is sexually transmitted was associated with higher levels of stigma and shame but not anxiety. Women who knew that HPV is sexually transmitted but not that it is highly prevalent had the highest scores for stigma and shame.

The findings of this study were supported by a structured interview study in 46 women in the United Kingdom, which indicated that lack of knowledge enhances anxiety after a positive HPV test result (Patel et al., 2018), and a study of 324 women in Serbia with an abnormal cytology result (Markovic-Denic et al., 2018), which found that awareness of a positive HPV test result increases anxiety and perceived risk of cancer and concern, but that knowledge about HPV decreased anxiety and concern. Slightly different results were obtained by a small educational intervention study in the USA in 50 women aged 30 years and older (Papa et al., 2009), which indicated that education may not alleviate the concern about developing cancer, and a randomized web-based survey in 3540 women in Norway (Burger et al., 2014), which indicated that a switch to HPV screening does not increase anxiety, irrespective of whether additional information about HPV is provided.

[The study outcomes suggest that awareness that HPV is sexually transmitted increases levels of anxiety, stigma, and shame, but that low levels can be retained by creating awareness of the high prevalence of HPV. Implementation of HPV testing should be accompanied by a well-designed education and communication strategy to explain what a positive HPV test result means.]

(d) Diagnostic harms of HPV testing as triage after an ASC-US or LSIL test result

The magnitude of the diagnostic harms of HPV testing as triage is indicated by the clinical specificity for the absence of CIN2+ and the number of referrals for colposcopy. Pooled estimates were calculated in a meta-analysis of 39 studies in women with ASC-US and 24 studies in women with LSIL in whom HPV triage was conducted by HC2 testing; the women subsequently underwent colposcopy and colposcopy-directed biopsies for histological verification (Arbyn et al., 2012, 2013a). The pooled specificity of HPV triage testing after an ASC-US result

for detection of CIN2+ was 58.3% (95% CI, 53.6–62.9%). There was considerable variation across the studies, with specificities ranging from 27% to 79%. The pooled specificity of HPV triage testing for the management of LSIL for detection of CIN2+ was only 27.8% (95% CI, 23.8–32.1%) and varied from 16% to 58% across studies. The proportion of referrals for colposcopy was 48.2% (95% CI, 43.7–52.6%) for ASC-US and 76.9% (95% CI, 73.5–80.2%) for LSIL.

Three well-documented studies in the meta-analyses that were large enough to enable comparison of different age cohorts were the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS) trial (Sherman et al., 2002), the NTCC trial (Ronco et al., 2007b), and the KPNC cohort (Castle et al., 2010). In women with ASC-US, the proportions of colposcopy referrals with HPV triage were 54% in the ALTS trial, 30% in the NTCC trial, and 35% in the KPNC cohort. In women with LSIL, the proportions of colposcopy referrals with HPV triage were 85% in the ALTS trial, 55% in the NTCC trial, and 84% in the KPNC cohort. In all three studies, the proportions of colposcopy referrals with HPV triage were dependent on age. In the ALTS trial, the proportion of women referred in the ASC-US subgroup decreased from 71% in women aged 18–22 years to 31% in women aged 29 years or older, whereas the referral proportion in the LSIL subgroup decreased only from 87% in women aged 18–22 years to 75% in women aged 29 years or older. In the NTCC trial, the referral proportions in the ASC-US subgroup were 46% in women aged 25–34 years and 25% in women aged 35–60 years, whereas the referral proportions in the LSIL subgroup were 72% in women aged 25–34 years and 41% in women aged 35–60 years. In the KPNC cohort, the referral proportions in the ASC-US subgroup decreased from 52% in women aged 30–34 years to 28% in women aged 60–64 years, and the referral proportions in the LSIL subgroup decreased

from 89% in women aged 30–34 years to 74% in women aged 60–64 years.

(e) Psychosocial and physical harms of self-collection versus clinician collection

HPV testing can be performed on a self-collected sample, and this may decrease the physical and psychosocial harms of the sample collection process. Several studies have collected information about the impact of the sample collection method on the acceptability and harms of HPV testing. A systematic review of 20 studies that assessed the acceptability of self-sampling, preferences, and experience with self-sampling (Huynh et al., 2010) indicated that discomfort and pain were not experienced in general. Most women in the studies also had a positive attitude towards self-sampling as a part of future screening. A concern observed in multiple studies was that women were unsure whether they had followed the testing procedure correctly and had greater confidence in the accuracy of the clinician collection. The preference for self-sampling was also observed in a larger systematic review and meta-analysis of 37 studies published in 1986–2014 that included more than 18 000 women in North America, South America, Europe, Africa, and Asia (Nelson et al., 2017). Most of the studies were in countries in North America, South America, and Europe; six studies were in Asian countries, and five studies were in African countries. Nine studies involved self-sampling at home. The pooled estimate of women reporting a preference for self-collection over clinician collection was 59% (95% CI, 48–69%). Reasons for preferring self-collection were that it is easy to use and that it is private, not embarrassing, convenient, and comfortable. Some women reported that they disliked self-collection because it was painful or physically uncomfortable, because it led to anxiety, or because of uncertainty about whether the sampling was done correctly. Some women indicated that they did not like touching themselves. One study in women in India,

Nicaragua, and Uganda also reported that most women surveyed (78%) preferred self-sampling; 75% reported that it was easy, although 52% were initially concerned about hurting themselves and 24% were worried about not getting a good sample. The acceptability of self-sampling was higher when providers prepared the women through education, when providers allowed women to examine the collection brush, and when providers were present during the self-collection process (Bansil et al., 2014).

Since the two systematic reviews were conducted, several studies have been published in which women invited for HPV screening were asked about their experiences and/or harms of self-sampling. Most of those studies were pilot implementation studies evaluating home-based self-sampling, sometimes with the involvement of a community health worker. An overview of recent studies is given here. A study of home-based HPV self-sampling in 746 non-responders to the screening programme in Australia randomized women to self-collection for HPV testing or a repeat invitation letter for a cervical cytology test at the clinic (Sultana et al., 2015). More than 90% of the women considered self-collection to be easier, more convenient, less embarrassing, and less uncomfortable; however, similar to studies in the meta-analyses, most women were unsure about the reliability of the HPV self-sampling test result. Most women (88%) preferred self-sampling at home because it was simple and did not require an appointment at the clinician's office. Similar findings were reported in a study of home-based self-sampling with involvement of a community health worker in 200 underscreened Aboriginal women in rural and remote communities in Australia, more than 90% of whom indicated that they were highly satisfied with the HPV self-sampling kit and the process involved (Dutton et al., 2020). Two large studies in Latin America – a study in 2616 women in Argentina invited for regular screening (Arrossi et al., 2016) and a study in 1867 underscreened women

in El Salvador (Maza et al., 2018) – assessed the attitude towards home-based self-sampling, both with involvement of a community health worker. Both studies reported that saving time was an additional reason to prefer self-sampling, in addition to the reasons that self-sampling is easy to perform and more comfortable and less embarrassing than clinician sampling. Maza et al. (2018) reported that feeling empowered was a reason for choosing self-sampling. Arrossi et al. (2016) reported, based on 433 women who chose clinician sampling instead of self-sampling, that the main reasons for not choosing self-sampling were trust in the clinician and the woman's fear of hurting herself. Another large self-sampling study included about 13 000 women in rural regions in Greece, who were recruited through a nationwide network of midwives (Chatzistamatiou et al., 2020). Women conducted self-sampling at home or at a general practitioner (GP) clinic and indicated minimal pain or discomfort and preference for self-collection when the test result is reliable. Testing at home was also preferred to self-sampling at a GP clinic. Positive experience of home-based self-sampling was also reported in other, smaller studies, including in women in rural Canada (Duke et al., 2015), Kenya (Oketch et al., 2019), Nigeria (Modibbo et al., 2017), and the United Republic of Tanzania (Bakiewicz et al., 2020), and in women in Japan with limited experience of tampon use (Hanley et al., 2016).

The role of home-based self-sampling in programmatic, regular screening is currently being discussed in several countries. In two recent studies, in the Netherlands (Polman et al., 2019c) and Sweden (Hermansson et al., 2020), HPV self-sampling was evaluated as a primary instrument in the setting of HPV-based screening without the use of an additional test for women with a negative HPV self-sampling result. In the study in the Netherlands (Polman et al., 2019c), experience was measured in routine screening in which women were randomized to HPV testing

on a self-collected versus clinician-collected sample. Responses were collected from 3835 women. Self-collection scored substantially lower on discomfort, pain, nervousness, and shame and higher on privacy compared with clinician collection. Trust in the test result was high with both self-collected and clinician-collected samples for HPV testing, irrespective of the HPV test result, although it was slightly higher for clinician sampling; 77% of the women reported that they preferred self-sampling for future screening. In the study in Sweden (Hermansson et al., 2020), in 868 women aged 60 years or older who had a positive HPV self-sampling result, 59% reported a preference for self-sampling versus 17% for clinician sampling. The main reasons for preferring self-sampling were that it is easy to perform and less embarrassing and less time-consuming than clinician sampling.

Information from non-responders and from clinicians can help to gain further insights into attitudes towards self-sampling. A study in underscreened women in the USA (Malone et al., 2020) compared attitudes in self-sampling kit returners (116 of 272 women invited) and non-returners (119 of 1083 women invited) and found no difference in attitude towards screening. The most common reason for non-return was low confidence in the woman's ability to correctly use the kit (Malone et al., 2020). In both groups, trust in the preventive effect of HPV screening against cancer was low. A randomized trial of HPV self-sampling in women in the USA that assessed attitudes in screened women and in clinicians (Mao et al., 2017) indicated that both screened women and clinicians expressed concerns about trust in the self-sampling test and valued the opportunity to discuss other health concerns with the clinician at the time of sampling.

Several individual studies compared attitudes and experiences with multiple sampling devices. In a study in non-responders in the Netherlands, the experiences of almost 10 000 women, to whom either a brush or lavage was offered, were compared (Bosgraaf et al., 2014). The experience of using the devices did not differ with respect to shame, feeling at ease, stress, discomfort, and pain, with levels similar to those observed in earlier studies. In a similarly designed study in Finland (Karjalainen et al., 2016), low discomfort and pain levels were reported for both devices. In a study in the KwaZulu-Natal region of South Africa in young women aged 16–22 years attending rural high schools (Mbatha et al., 2017), a choice between home-based self-sampling with a swab or a brush and clinician sampling was offered to all women. Most women expressed a preference for self-sampling (56%) compared with clinician sampling (44%). Pain was reported less often for the swab than for the brush, and the swab was preferred to the brush by most women who favoured self-sampling. However, in a study in Norway in women with a positive clinician-based hrHPV test, in which home-based self-sampling with a swab and a brush was subsequently offered to all women (Leinonen et al., 2018), both the swab and the brush were rated very positively, but the brush was reported as slightly easier to use and more comfortable.

[This indicates that although the experience was in general very positive, the preferred self-sampling method may vary across populations.]

References

Agorastos T, Chatzistamatiou K, Katsamagkas T, Koliopoulos G, Daponte A, Constantinidis T, et al.; HERMES study group (2015). Primary screening for cervical cancer based on high-risk human papillomavirus (HPV) detection and HPV 16 and HPV 18 genotyping, in comparison to cytology. *PLoS One.* 10(3):e0119755. doi:10.1371/journal.pone.0119755 PMID:25793281

Agorastos T, Chatzistamatiou K, Moysiadis T, Kaufmann AM, Skenderi A, Lekka I, et al. (2017). Human papillomavirus E7 protein detection as a method of triage to colposcopy of HPV positive women, in comparison to genotyping and cytology. Final results of the PIPAVIR

study. *Int J Cancer*. 141(3):519–30. doi:10.1002/ijc.30761 PMID:28470689

Agorastos T, Dinas K, Lloveras B, de Sanjose S, Kornegay JR, Bonti H, et al. (2005). Human papillomavirus testing for primary screening in women at low risk of developing cervical cancer. The Greek experience. *Gynecol Oncol*. 96(3):714–20. doi:10.1016/j.ygyno.2004.11.042 PMID:15721416

Aitken CA, van Agt HME, Siebers AG, van Kemenade FJ, Niesters HGM, Melchers WJG, et al. (2019). Introduction of primary screening using high-risk HPV DNA detection in the Dutch cervical cancer screening programme: a population-based cohort study. *BMC Med*. 17(1):228. doi:10.1186/s12916-019-1460-0 PMID:31829241

Almonte M, Murillo R, Sánchez GI, González P, Ferrera A, Picconi MA, et al. (2020). Multicentric study of cervical cancer screening with human papillomavirus testing and assessment of triage methods in Latin America: the ESTAMPA screening study protocol. *BMJ Open*. 10(5):e035796. doi:10.1136/bmjopen-2019-035796 PMID:32448795

Andreassen T, Hansen BT, Engesæter B, Hashim D, Støer NC, Tropé A, et al. (2019). Psychological effect of cervical cancer screening when changing primary screening method from cytology to high-risk human papilloma virus testing. *Int J Cancer*. 145(1):29–39. doi:10.1002/ijc.32067 PMID:30549273

Anhang R, Nelson JA, Telerant R, Chiasson MA, Wright TC Jr (2005). Acceptability of self-collection of specimens for HPV DNA testing in an urban population. *J Womens Health (Larchmt)*. 14(8):721–8. doi:10.1089/jwh.2005.14.721 PMID:16232104

Anhang R, Wright TC Jr, Smock L, Goldie SJ (2004). Women's desired information about human papillomavirus. *Cancer*. 100(2):315–20. doi:10.1002/cncr.20007 PMID:14716766

Arbyn M, Hillemanns P (2018). HPV assays validated for primary cervical cancer screening. *HPV World*. 55:6–9. Available from: https://www.hpvworld.com/articles/hpv-assays-validated-for-primary-cervical-cancer-screening/.

Arbyn M, Rezhake R, Yuill S, Canfell K (2020). Triage of HPV-positive women in Norway using cytology, HPV16/18 genotyping and HPV persistence. *Br J Cancer*. 122(11):1577–9. doi:10.1038/s41416-020-0787-9 PMID:32242099

Arbyn M, Roelens J, Cuschieri K, Cuzick J, Szarewski A, Ratnam S, et al. (2013b). The APTIMA HPV assay versus the Hybrid Capture 2 test in triage of women with ASC-US or LSIL cervical cytology: a meta-analysis of the diagnostic accuracy. *Int J Cancer*. 132(1):101–8. doi:10.1002/ijc.27636 PMID:22610699

Arbyn M, Roelens J, Simoens C, Buntinx F, Paraskevaidis E, Martin-Hirsch PPL, et al. (2013a). Human papillomavirus testing versus repeat cytology for triage of

minor cytological cervical lesions. *Cochrane Database Syst Rev*. 2013(3):CD008054. doi:10.1002/14651858.CD008054.pub2 PMID:23543559

Arbyn M, Ronco G, Anttila A, Meijer CJLM, Poljak M, Ogilvie G, et al. (2012). Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. [Erratum in: Vaccine. 2013 31(52):6266] *Vaccine*. 30(Suppl 5):F88–99. doi:10.1016/j.vaccine.2012.06.095 PMID:23199969

Arbyn M, Sankaranarayanan R, Muwonge R, Keita N, Dolo A, Mbalawa CG, et al. (2008). Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. *Int J Cancer*. 123(1):153–60. doi:10.1002/ijc.23489 PMID:18404671

Arbyn M, Smith SB, Temin S, Sultana F, Castle P; Collaboration on Self-Sampling and HPV Testing (2018). Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. *BMJ*. 363:k4823. doi:10.1136/bmj.k4823 PMID:30518635

Arbyn M, Snijders PJF, Meijer CJLM, Berkhof J, Cuschieri K, Kocjan BJ, et al. (2015). Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening? *Clin Microbiol Infect*. 21(9):817–26. doi:10.1016/j.cmi.2015.04.015 PMID:25936581

Arbyn M, Verdoodt F, Snijders PJF, Verhoef VMJ, Suonio E, Dillner L, et al. (2014). Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol*. 15(2):172–83. doi:10.1016/S1470-2045(13)70570-9 PMID:24433684

Arbyn M, Xu L, Verdoodt F, Cuzick J, Szarewski A, Belinson JL, et al. (2017). Genotyping for human papillomavirus types 16 and 18 in women with minor cervical lesions: a systematic review and meta-analysis. *Ann Intern Med*. 166(2):118–27. doi:10.7326/M15-2735 PMID:27842420

Arrossi S, Almonte M, Herrero R, Gago J, Sánchez Antelo V, Szwarc L, et al. (2020). Psycho-social impact of positive human papillomavirus testing in Jujuy, Argentina results from the Psycho-Estampa study. *Prev Med Rep*. 18:101070. doi:10.1016/j.pmedr.2020.101070 PMID:32257775

Arrossi S, Paolino M, Laudi R, Gago J, Campanera A, Marín O, et al. (2019). Programmatic human papillomavirus testing in cervical cancer prevention in the Jujuy Demonstration Project in Argentina: a population-based, before-and-after retrospective cohort study. *Lancet Glob Health*. 7(6):e772–83. doi:10.1016/S2214-109X(19)30048-8 PMID:31097279

Arrossi S, Ramos S, Straw C, Thouyaret L, Orellana L (2016). HPV testing: a mixed-method approach to understand why women prefer self-collection in a middle-income country. *BMC Public Health*. 16(1):832. doi:10.1186/s12889-016-3474-2 PMID:27538390

Asthana S, Labani S (2015). Adjunct screening of cervical or vaginal samples using careHPV testing with Pap and aided visual inspection for detecting high-grade cervical intraepithelial neoplasia. *Cancer Epidemiol.* 39(1):104–8. doi:10.1016/j.canep.2014.11.006 PMID:25548076

Bakiewicz A, Rasch V, Mwaiselage J, Linde DS (2020). "The best thing is that you are doing it for yourself" – perspectives on acceptability and feasibility of HPV self-sampling among cervical cancer screening clients in Tanzania: a qualitative pilot study. *BMC Womens Health.* 20(1):65. doi:10.1186/s12905-020-00917-7 PMID:32234028

Bansil P, Wittet S, Lim JL, Winkler JL, Paul P, Jeronimo J (2014). Acceptability of self-collection sampling for HPV-DNA testing in low-resource settings: a mixed methods approach. *BMC Public Health.* 14(1):596. doi:10.1186/1471-2458-14-596 PMID:24927941

Basu P, Mittal S, Banerjee D, Singh P, Panda C, Dutta S, et al. (2015). Diagnostic accuracy of VIA and HPV detection as primary and sequential screening tests in a cervical cancer screening demonstration project in India. *Int J Cancer.* 137(4):859–67. doi:10.1002/ijc.29458 PMID:25631198

Belinson J, Qiao YL, Pretorius R, Zhang WH, Elson P, Li L, et al. (2001). Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. [Erratum in: Gynecol Oncol. 2002 84(2):355] *Gynecol Oncol.* 83(2):439–44. doi:10.1006/gyno.2001.6370 PMID:11606114

Belinson JL, Qiao YL, Pretorius RG, Zhang WH, Rong SD, Huang MN, et al. (2003). Shanxi Province Cervical Cancer Screening Study II: self-sampling for high-risk human papillomavirus compared to direct sampling for human papillomavirus and liquid based cervical cytology. Int J Gynecol Cancer. 13(6):819–26. doi:10.1136/ijgc-00009577-200311000-00013 PMID:14675319

Belinson SE, Wulan N, Li R, Zhang W, Rong X, Zhu Y, et al. (2010). SNIPER: a novel assay for human papillomavirus testing among women in Guizhou, China. *Int J Gynecol Cancer.* 20(6):1006–10. doi:10.1111/IGC.0b013e3181e73092 PMID:20683409

Bennett KF, Waller J, Ryan M, Bailey JV, Marlow LAV (2019). The psychosexual impact of testing positive for high-risk cervical human papillomavirus (HPV): a systematic review. *Psychooncology.* 28(10):1959–70. doi:10.1002/pon.5198 PMID:31411787

Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM (2010). Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology.* 401(1):70–9. doi:10.1016/j.virol.2010.02.002 PMID:20206957

Bian ML, Cheng JY, Ma L, Cong X, Liu J, Chen Y, et al. (2013). Evaluation of the detection of 14 high-risk human papillomaviruses with HPV 16 and HPV 18 genotyping for cervical cancer screening. *Exp Ther Med.* 6(5):1332–6. doi:10.3892/etm.2013.1309 PMID:24223668

Bigras G, de Marval F (2005). The probability for a Pap test to be abnormal is directly proportional to HPV viral load: results from a Swiss study comparing HPV testing and liquid-based cytology to detect cervical cancer precursors in 13,842 women. *Br J Cancer.* 93(5):575–81. doi:10.1038/sj.bjc.6602728 PMID:16136031

Blatt AJ, Kennedy R, Luff RD, Austin RM, Rabin DS (2015). Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol.* 123(5):282–8. doi:10.1002/cncy.21544 PMID:25864682

Bobdey S, Balasubramanium G, Kumar A, Jain A (2015). Cancer screening: should cancer screening be essential component of primary health care in developing countries? *Int J Prev Med.* 6:56. PMID:26236443

Bobdey S, Sathwara J, Jain A, Balasubramaniam G (2016). Burden of cervical cancer and role of screening in India. *Indian J Med Paediatr Oncol.* 37(4):278–85. doi:10.4103/0971-5851.195751 PMID:28144096

Bosgraaf RP, Ketelaars PJW, Verhoef VMJ, Massuger LFAG, Meijer CJLM, Melchers WJG, et al. (2014). Reasons for non-attendance to cervical screening and preferences for HPV self-sampling in Dutch women. *Prev Med.* 64:108–13. doi:10.1016/j.ypmed.2014.04.011 PMID:24736093

Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al.; WHO International Agency for Research on Cancer Monograph Working Group (2009). A review of human carcinogens – Part B: biological agents. *Lancet Oncol.* 10(4):321–2. doi:10.1016/S1470-2045(09)70096-8 PMID:19350698

Bridges KW, Goldberg DP (1986). The validation of the GHQ-28 and the use of the MMSE in neurological in-patients. *Br J Psychiatry.* 148(5):548–53. doi:10.1192/bjp.148.5.548 PMID:3779225

Bulkmans NWJ, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJP, Bulk S, et al. (2007). Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet.* 370(9601):1764–72. doi:10.1016/S0140-6736(07)61450-0 PMID:17919718

Bulkmans NWJ, Rozendaal L, Snijders PJF, Voorhorst FJ, Boeke AJP, Zandwijken GRJ, et al. (2004). POBASCAM, a population-based randomized controlled trial for implementation of high-risk HPV testing in cervical screening: design, methods and baseline data of 44,102 women. *Int J Cancer.* 110(1):94–101. doi:10.1002/ijc.20076 PMID:15054873

Burger EA, Nygård M, Gyrd-Hansen D, Moger TA, Kristiansen IS (2014). Does the primary screening test influence women's anxiety and intention to screen for cervical cancer? A randomized survey of Norwegian women. *BMC Public Health*. 14(1):360. doi:10.1186/1471-2458-14-360 PMID:24735469

Campos NG, Alfaro K, Maza M, Sy S, Melendez M, Masch R, et al. (2020). The cost-effectiveness of human papillomavirus self-collection among cervical cancer screening non-attenders in El Salvador. *Prev Med*. 131:105931. doi:10.1016/j.ypmed.2019.105931 PMID:31765712

Campos NG, Tsu V, Jeronimo J, Njama-Meya D, Mvundura M, Kim JJ (2017). Cost-effectiveness of an HPV self-collection campaign in Uganda: comparing models for delivery of cervical cancer screening in a low-income setting. *Health Policy Plan*. 32(7):956–68. doi:10.1093/heapol/czw182 PMID:28369405

Canfell K, Caruana M, Gebski V, Darlington-Brown J, Heley S, Brotherton J, et al. (2017). Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: results of the Compass pilot randomised trial. *PLoS Med*. 14(9):e1002388. doi:10.1371/journal.pmed.1002388 PMID:28926579

Canfell K, Saville M, Caruana M, Gebski V, Darlington-Brown J, Brotherton J, et al. (2018). Protocol for Compass: a randomised controlled trial of primary HPV testing versus cytology screening for cervical cancer in HPV-unvaccinated and vaccinated women aged 25–69 years living in Australia. [Erratum in: BMJ Open. 2018 8(3):e016700corr1] *BMJ Open*. 8(1):e016700. doi:10.1136/bmjopen-2017-016700 PMID:29374658

Cárdenas-Turanzas M, Nogueras-Gonzalez GM, Scheurer ME, Adler-Storthz K, Benedet JL, Beck JR, et al. (2008). The performance of human papillomavirus high-risk DNA testing in the screening and diagnostic settings. *Cancer Epidemiol Biomarkers Prev*. 17(10):2865–71. doi:10.1158/1055-9965.EPI-08-0137 PMID:18843032

Castle PE (2015). Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol*. 123(9):566. doi:10.1002/cncy.21572 PMID:26179787

Castle PE, Fetterman B, Thomas Cox J, Shaber R, Poitras N, Lorey T, et al. (2010). The age-specific relationships of abnormal cytology and human papillomavirus DNA results to the risk of cervical precancer and cancer. *Obstet Gynecol*. 116(1):76–84. doi:10.1097/AOG.0b013e3181e3e719 PMID:20567171

Castle PE, Kinney WK, Xue X, Cheung LC, Gage JC, Poitras NE, et al. (2019). Role of screening history in clinical meaning and optimal management of positive cervical screening results. *J Natl Cancer Inst*. 111(8):820–7. doi:10.1093/jnci/djy192 PMID:30576462

Castle PE, Kinney WK, Xue X, Cheung LC, Gage JC, Zhao FH, et al. (2018). Effect of several negative rounds of human papillomavirus and cytology co-testing on safety against cervical cancer: an observational cohort study. *Ann Intern Med*. 168(1):20–9. doi:10.7326/M17-1609 PMID:29181509

Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM (2011). Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. *Lancet Oncol*. 12(9):880–90. doi:10.1016/S1470-2045(11)70188-7 PMID:21865084

Chan KKL, Liu SS, Wei N, Ngu SF, Chu MMY, Tse KY, et al. (2020). Primary HPV testing with cytology versus cytology alone in cervical screening – a prospective randomized controlled trial with two rounds of screening in a Chinese population. *Int J Cancer*. 147(4):1152–62. doi:10.1002/ijc.32861 PMID:31922265

Chatzistamatiou K, Vrekoussis T, Tsertanidou A, Moysiadis T, Mouchtaropoulou E, Pasentsis K, et al. (2020). Acceptability of self-sampling for human papillomavirus-based cervical cancer screening. *J Womens Health (Larchmt)*. 29(11):1447–56. doi:10.1089/jwh.2019.8258 PMID:32757997

Chen C, Yang Z, Li Z, Li L (2012). Accuracy of several cervical screening strategies for early detection of cervical cancer: a meta-analysis. *Int J Gynecol Cancer*. 22(6):908–21. doi:10.1097/IGC.0b013e318256e5e4 PMID:22672987

Cheung LC, Egemen D, Chen X, Katki HA, Demarco M, Wiser AL, et al. (2020). 2019 ASCCP risk-based management consensus guidelines: methods for risk estimation, recommended management, and validation. *J Low Genit Tract Dis*. 24(2):90–101. doi:10.1097/LGT.0000000000000528 PMID:32243306

Choi JW, Kim Y, Lee JH, Kim YS (2016). The clinical performance of primary HPV screening, primary HPV screening plus cytology cotesting, and cytology alone at a tertiary care hospital. *Cancer Cytopathol*. 124(2):144–52. doi:10.1002/cncy.21632 PMID:26457676

Clavel C, Masure M, Bory JP, Putaud I, Mangeonjean C, Lorenzato M, et al. (2001). Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer*. 84(12):1616–23. doi:10.1054/bjoc.2001.1845 PMID:11401314

Coldman AJ, van Niekerk D, Krajden M, Smith LW, Cook D, Gondara L, et al. (2020). Disease detection at the 48-month exit round of the HPV FOCAL cervical cancer screening trial in women per-protocol eligible for routine screening. *Int J Cancer*. 146(7):1810–8. doi:10.1002/ijc.32524 PMID:31245842

Cook DA, Smith LW, Law J, Mei W, van Niekerk DJ, Ceballos K, et al. (2017). Aptima HPV Assay versus Hybrid Capture® 2 HPV test for primary cervical

cancer screening in the HPV FOCAL trial. *J Clin Virol*. 87:23–9. doi:10.1016/j.jcv.2016.12.004 PMID:27988420

Cook DA, Smith LW, Law JH, Mei W, Gondara L, van Niekerk DJ, et al. (2018). Comparative performance of human papillomavirus messenger RNA versus DNA screening tests at baseline and 48 months in the HPV FOCAL trial. *J Clin Virol*. 108:32–7. doi:10.1016/j.jcv.2018.09.004 PMID:30223252

Cotton SC, Sharp L, Little J, Duncan I, Alexander L, Cruickshank ME, et al.; TOMBOLA group (2006). Trial of management of borderline and other low-grade abnormal smears (TOMBOLA): trial design. *Contemp Clin Trials*. 27(5):449–71. doi:10.1016/j.cct.2006.04.001 PMID:16765101

Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, et al. (2003). Management of women who test positive for high-risk types of human papillomavirus: the HART study. *Lancet*. 362(9399):1871–6. doi:10.1016/S0140-6736(03)14955-0 PMID:14667741

Daley EM, Perrin KM, McDermott RJ, Vamos CA, Rayko HL, Packing-Ebuen JL, et al. (2010). The psychosocial burden of HPV: a mixed-method study of knowledge, attitudes and behaviors among HPV+ women. *J Health Psychol*. 15(2):279–90. doi:10.1177/1359105309351249 PMID:20207671

de Cremoux P, Coste J, Sastre-Garau X, Thioux M, Bouillac C, Labbé S, et al.; French Society of Clinical Cytology Study Group (2003). Efficiency of the Hybrid Capture 2 HPV DNA test in cervical cancer screening. A study by the French Society of Clinical Cytology. *Am J Clin Pathol*. 120(4):492–9. doi:10.1309/XFUCPP6M5XUA94B8 PMID:14560561

Del Mistro A, Giorgi Rossi P, Frayle H, Pasquale L, Campari C, Ronco G, et al. (2019). Five-year risk of CIN3 after short-term HPV-DNA negativity in cytology-negative women: a population-based cohort study. *BJOG*. 126(11):1365–71. doi:10.1111/1471-0528.15893 PMID:31356722

Demarco M, Egemen D, Raine-Bennett TR, Cheung LC, Befano B, Poitras NE, et al. (2020). A study of partial human papillomavirus genotyping in support of the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis*. 24(2):144–7. doi:10.1097/LGT.0000000000000530 PMID:32243309

Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC Jr (2005). Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA*. 294(17):2173–81. doi:10.1001/jama.294.17.2173 PMID:16264158

Denny L, Kuhn L, Hu CC, Tsai WY, Wright TC Jr (2010). Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. *J Natl Cancer Inst*. 102(20):1557–67. doi:10.1093/jnci/djq342 PMID:20884893

Depuydt CE, Makar AP, Ruymbeke MJ, Benoy IH, Vereecken AJ, Bogers JJ (2011). BD-ProExC as adjunct molecular marker for improved detection of CIN2+ after HPV primary screening. *Cancer Epidemiol Biomarkers Prev*. 20(4):628–37. doi:10.1158/1055-9965.EPI-10-0818 PMID:21297040

Dijkstra MG, van Zummeren M, Rozendaal L, van Kemenade FJ, Helmerhorst TJM, Snijders PJF, et al. (2016). Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. *BMJ*. 355:i4924. doi:10.1136/bmj.i4924 PMID:27702796

Dillner J, Arbyn M, Unger E, Dillner L (2011). Monitoring of human papillomavirus vaccination. *Clin Exp Immunol*. 163(1):17–25. doi:10.1111/j.1365-2249.2010.04268.x PMID:21062269

Dillner J, Rebolj M, Birembaut P, Petry KU, Szarewski A, Munk C, et al. (2008). Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ*. 337:a1754. doi:10.1136/bmj.a1754 PMID:18852164

Duke P, Godwin M, Ratnam S, Dawson L, Fontaine D, Lear A, et al. (2015). Effect of vaginal self-sampling on cervical cancer screening rates: a community-based study in Newfoundland. *BMC Womens Health*. 15(1):47. doi:10.1186/s12905-015-0206-1 PMID:26060041

Dutton T, Marjoram J, Burgess S, Montgomery L, Vail A, Callan N, et al. (2020). Uptake and acceptability of human papillomavirus self-sampling in rural and remote Aboriginal communities: evaluation of a nurse-led community engagement model. *BMC Health Serv Res*. 20(1):398. doi:10.1186/s12913-020-05214-5 PMID:32393243

Dyer N, Young L, Ott S (2016). Artifacts in the data of Hu et al. *Nat Genet*. 48(1):2–4. doi:10.1038/ng.3392 PMID:26711106

Eklund C, Forslund O, Wallin KL, Dillner J (2014). Global improvement in genotyping of human papillomavirus DNA: the 2011 HPV LabNet International Proficiency Study. *J Clin Microbiol*. 52(2):449–59. doi:10.1128/JCM.02453-13 PMID:24478473

El-Zein M, Bouten S, Louvanto K, Gilbert L, Gotlieb W, Hemmings R, et al.; CASSIS Study Group (2018). Validation of a new HPV self-sampling device for cervical cancer screening: the Cervical and Self-Sample In Screening (CASSIS) study. *Gynecol Oncol*. 149(3):491–7. doi:10.1016/j.ygyno.2018.04.004 PMID:29678360

Elfgren K, Elfström KM, Naucler P, Arnheim-Dahlström L, Dillner J (2017). Management of women with human papillomavirus persistence: long-term follow-up of a randomized clinical trial. *Am J Obstet Gynecol*. 216(3):264.e1–7. doi:10.1016/j.ajog.2016.10.042 PMID:27825977

Elfström KM, Smelov V, Johansson AL, Eklund C, Nauclér P, Arnheim-Dahlström L, et al. (2014). Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial. *BMJ*. 348:g130. doi:10.1136/bmj.g130 PMID:24435414

Ferreccio C, Barriga MI, Lagos M, Ibáñez C, Poggi H, González F, et al. (2013). Screening trial of human papillomavirus for early detection of cervical cancer in Santiago, Chile. *Int J Cancer*. 132(4):916–23. doi:10.1002/ijc.27662 PMID:22684726

Fokom-Domgue J, Combescure C, Fokom-Defo V, Tebeu PM, Vassilakos P, Kengne AP, et al. (2015). Performance of alternative strategies for primary cervical cancer screening in sub-Saharan Africa: systematic review and meta-analysis of diagnostic test accuracy studies. *BMJ*. 351:h3084. doi:10.1136/bmj.h3084 PMID:26142020

Forslund O, Elfström KM, Lamin H, Dillner J (2019). HPV-mRNA and HPV-DNA detection in samples taken up to seven years before severe dysplasia of cervix uteri. *Int J Cancer*. 144(5):1073–81. doi:10.1002/ijc.31819 PMID:30125346

Gage JC, Schiffman M, Katki HA, Castle PE, Fetterman B, Wentzensen N, et al. (2014). Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J Natl Cancer Inst*. 106(8):dju153. doi:10.1093/jnci/dju153 PMID:25038467

Garcés-Palacio IC, Ramos-Jaraba SM, Rubio-León DC (2018). Health beliefs associated with the follow-up of Pap smear abnormalities among low-income women in Medellín, Colombia. *J Cancer Educ*. 33(2):417–23. doi:10.1007/s13187-017-1172-0 PMID:28120138

Garcés-Palacio IC, Sanchez GI, Baena Zapata A, Córdoba Sánchez V, Urrea Cosme Y, Rodríguez Zabala D, et al. (2020). Psychosocial impact of inclusion of HPV test on the management of women with atypical squamous cells of undetermined significance: a study within a randomised pragmatic trial in a middle-income country. *Psychol Health*. 35(6):750–69. doi:10.1080/08870446.2019.1678749 PMID:31625399

Garratt AM, Torgerson DJ, Wyness J, Hall MH, Reid DM (1995). Measuring sexual functioning in premeno-pausal women. *Br J Obstet Gynaecol*. 102(4):311–6. doi:10.1111/j.1471-0528.1995.tb09138.x PMID:7612515

Gen-Probe (2011). APTIMA® HPV Assay. For in vitro diagnostic use. San Diego (CA), USA: Gen-Probe Inc. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100042c.pdf.

Giorgi Rossi P, Ronco G, Dillner J, Elfström KM, Snijders PJF, Arbyn M, et al.; New Technologies for Cervical Cancer Group (2016). Why follow-back studies should be interpreted cautiously: the case of an HPV-negative cervical lesion. *Cancer Cytopathol*. 124(1):66–7. doi:10.1002/cncy.21622 PMID:26356132

Gravitt PE, Paul P, Katki HA, Vendantham H, Ramakrishna G, Sudula M, et al.; CATCH Study Team (2010). Effectiveness of VIA, Pap, and HPV DNA testing in a cervical cancer screening program in a peri-urban community in Andhra Pradesh, India. *PLoS One*. 5(10):e13711. doi:10.1371/journal.pone.0013711 PMID:21060889

Gustinucci D, Giorgi Rossi P, Cesarini E, Broccolini M, Bulletti S, Carlani A, et al. (2016). Use of cytology, E6/E7 mRNA, and p16INK4a-Ki-67 to define the management of human papillomavirus (HPV)-positive women in cervical cancer screening. *Am J Clin Pathol*. 145(1):35–45. doi:10.1093/ajcp/aqv019 PMID:26712869

Haedicke J, Iftner T (2016). A review of the clinical performance of the Aptima HPV assay. *J Clin Virol*. 76(Suppl 1):S40–8. doi:10.1016/j.jcv.2015.10.027 PMID:26614686

Han L, Chang X, Song P, Gao L, Zhang Y, An L, et al. (2020). An on-going study of three different cervical cancer screening strategies based on primary healthcare facilities in Beijing China. *J Infect Public Health*. 13(4):577–83. doi:10.1016/j.jiph.2019.09.003 PMID:31564529

Hanley SJ, Fujita H, Yokoyama S, Kunisawa S, Tamakoshi A, Dong P, et al. (2016). HPV self-sampling in Japanese women: a feasibility study in a population with limited experience of tampon use. *J Med Screen*. 23(3):164–70. doi:10.1177/0969141315625702 PMID:26919866

Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JAC (2007). A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics*. 8(2):239–51. doi:10.1093/biostatistics/kxl004 PMID:16698768

Harbord RM, Whiting P (2009). metandi: Meta-analysis of diagnostic accuracy using hierar-chical logistic regression. *Stata J*. 9(2):211–29. doi:10.1177/1536867X0900900203

HAS (2019). Evaluation de la recherche des papilloma-virus humains (HPV) en dépistage primaire des lésions précancéreuses et cancéreuses du col de l'utérus et de la place du double immuno-marquage p16/Ki67. Saint-Denis La Plaine, France: Haute Autorité de Santé. [in French] Available from: https://www.has-sante.fr/upload/docs/application/pdf/2019-09/rapport_hpv_2019-09-09_14-20-44_251.pdf.

Herbert A, Arbyn M, Bergeron C (2008). Why CIN3 and CIN2 should be distinguished on histological reports. *Cytopathology*. 19(1):63–4. doi:10.1111/j.1365-2303.2006.00539.x PMID:18205632

Hermansson RS, Olovsson M, Gustavsson C, Lindström AK (2020). Elderly women's experiences of self-sampling for HPV testing. *BMC Cancer*. 20(1):473. doi:10.1186/s12885-020-06977-0 PMID:32456679

Holt HK, Zhang L, Zhao FH, Hu SY, Zhao XL, Zhang X, et al. (2017). Evaluation of multiple primary and combi-nation screening strategies in postmenopausal women for detection of cervical cancer in China. *Int J Cancer*. 140(3):544–54. doi:10.1002/ijc.30468 PMID:27727464

Horn J, Denecke A, Luyten A, Rothe B, Reinecke-Lüthge A, Mikolajczyk R, et al. (2019). Reduction of cervical cancer incidence within a primary HPV screening pilot project (WOLPHSCREEN) in Wolfsburg, Germany. *Br J Cancer.* 120(10):1015–22. doi:10.1038/s41416-019-0453-2 PMID:30988395

Hovland S, Arbyn M, Lie AK, Ryd W, Borge B, Berle EJ, et al. (2010). A comprehensive evaluation of the accuracy of cervical pre-cancer detection methods in a high-risk area in East Congo. *Br J Cancer.* 102(6):957–65. doi:10.1038/sj.bjc.6605594 PMID:20197765

Hsu YY, Wang WM, Fetzer SJ, Cheng YM, Hsu KF (2018). Longitudinal psychosocial adjustment of women to human papillomavirus infection. *J Adv Nurs.* 74(11):2523–32. doi:10.1111/jan.13725 PMID:29845650

Hu Z, Zhu D, Wang W, Li W, Jia W, Zeng X, et al. (2015). Genome-wide profiling of HPV integration in cervical cancer identifies clustered genomic hot spots and a potential microhomology-mediated integration mechanism. *Nat Genet.* 47(2):158–63. doi:10.1038/ng.3178 PMID:25581428

Huh WK, Ault KA, Chelmow D, Davey DD, Goulart RA, Garcia FA, et al. (2015). Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Obstet Gynecol.* 125(2):330–7. doi:10.1097/AOG.0000000000000669 PMID:25569009

Huynh J, Howard M, Lytwyn A (2010). Self-collection for vaginal human papillomavirus testing: systematic review of studies asking women their perceptions. *J Low Genit Tract Dis.* 14(4):356–62. doi:10.1097/LGT.0b013e3181dc115b PMID:20885165

IARC (2005). Cervix cancer screening. *IARC Handb Cancer Prev.* 10:1–302. Available from: https://publications.iarc.fr/380.

IARC (2007). Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum.* 90:1–670. Available from: https://publications.iarc.fr/108 PMID:18354839

IARC (2012). Biological agents. *IARC Monogr Eval Carcinog Risks Hum.* 100B:1–475. Available from: https://publications.iarc.fr/119 PMID:23189750

Iftner T, Becker S, Neis KJ, Castanon A, Iftner A, Holz B, et al. (2015). Head-to-head comparison of the RNA-based Aptima human papillomavirus (HPV) assay and the DNA-based Hybrid Capture 2 HPV test in a routine screening population of women aged 30 to 60 years in Germany. *J Clin Microbiol.* 53(8):2509–16. doi:10.1128/JCM.01013-15 PMID:26019212

Iftner T, Neis KJ, Castanon A, Landy R, Holz B, Woll-Herrmann A, et al. (2019). Longitudinal clinical performance of the RNA-based Aptima human papillomavirus (AHPV) assay in comparison to the DNA-based Hybrid Capture 2 HPV test in two consecutive screening rounds with a 6-year interval in Germany. *J Clin Microbiol.* 57(1):e01177–18. doi:10.1128/JCM.01177-18 PMID:30355760

Iftner T, Villa LL (2003). Chapter 12: human papillomavirus technologies. *J Natl Cancer Inst Monogr.* 2003(31): 80–8. doi:10.1093/oxfordjournals.jncimonographs.a003487 PMID:12807950

Isidean SD, Mayrand MH, Ramanakumar AV, Gilbert L, Reid SL, Rodrigues I, et al.; CCCaST Study Group (2016). Human papillomavirus testing versus cytology in primary cervical cancer screening: end-of-study and extended follow-up results from the Canadian Cervical Cancer Screening Trial. *Int J Cancer.* 139(11):2456–66. doi:10.1002/ijc.30385 PMID:27538188

Isidean SD, Mayrand MH, Ramanakumar AV, Rodrigues I, Ferenczy A, Ratnam S, et al.; CCCaST Study Group (2017). Comparison of triage strategies for HPV-positive women: Canadian Cervical Cancer Screening Trial results. *Cancer Epidemiol Biomarkers Prev.* 26(6):923–9. doi:10.1158/1055-9965.EPI-16-0705 PMID:28096198

Islam JY, Mutua MM, Kabare E, Manguro G, Hudgens MG, Poole C, et al. (2020). High-risk human papillomavirus messenger RNA testing in wet and dry self-collected specimens for high-grade cervical lesion detection in Mombasa, Kenya. *Sex Transm Dis.* 47(7):464–72. doi:10.1097/OLQ.0000000000001167 PMID:32168174

Johnson CY, Sharp L, Cotton SC, Harris CA, Gray NM, Little J; TOMBOLA Group (2011). Human papillomavirus infection and anxiety: analyses in women with low-grade cervical cytological abnormalities unaware of their infection status. *PLoS One.* 6(6):e21046. doi:10.1371/journal.pone.0021046 PMID:21698168

Josefsson A, Livak K, Gyllensten U (1999). Detection and quantitation of human papillomavirus by using the fluorescent 5′ exonuclease assay. *J Clin Microbiol.* 37(3):490–6. doi:10.1128/JCM.37.3.490-496.1999 PMID:9986801

Kahn JA, Slap GB, Bernstein DI, Kollar LM, Tissot AM, Hillard PA, et al. (2005). Psychological, behavioral, and interpersonal impact of human papillomavirus and Pap test results. *J Womens Health (Larchmt).* 14(7):650–9. doi:10.1089/jwh.2005.14.650 PMID:16181021

Karjalainen L, Anttila A, Nieminen P, Luostarinen T, Virtanen A (2016). Self-sampling in cervical cancer screening: comparison of a brush-based and a lavage-based cervicovaginal self-sampling device. *BMC Cancer.* 16(1):221. doi:10.1186/s12885-016-2246-9 PMID:26979237

Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, et al. (2011). Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol.* 12(7):663–72. doi:10.1016/S1470-2045(11)70145-0 PMID:21684207

Kaufman HW, Alagia DP, Chen Z, Onisko A, Austin RM (2020). Contributions of liquid-based (Papanicolaou) cytology and human papillomavirus testing in cotesting for detection of cervical cancer and precancer

in the United States. *Am J Clin Pathol*. 154(4):510–6. doi:10.1093/ajcp/aqaa074 PMID:32637991

Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, et al.; ARTISTIC Trial Study Group (2009b). ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. *Health Technol Assess*. 13(51):iii–iv, 1–150. doi:10.3310/hta13510 PMID:19891902

Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al. (2009a). HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol*. 10(7):672–82. doi:10.1016/S1470-2045(09)70156-1 PMID:19540162

Kitchener HC, Canfell K, Gilham C, Sargent A, Roberts C, Desai M, et al. (2014). The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. *Health Technol Assess*. 18(23):1–196. doi:10.3310/hta18230 PMID:24762804

Kitchener HC, Fletcher I, Roberts C, Wheeler P, Almonte M, Maguire P (2008). The psychosocial impact of human papillomavirus testing in primary cervical screening – a study within a randomized trial. *Int J Gynecol Cancer*. 18(4):743–8. doi:10.1111/j.1525-1438.2007.01113.x PMID:17944916

Kitchener HC, Gilham C, Sargent A, Bailey A, Albrow R, Roberts C, et al. (2011). A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. *Eur J Cancer*. 47(6):864–71. doi:10.1016/j.ejca.2011.01.008 PMID:21334200

Kocsis A, Takács T, Jeney C, Schaff Z, Koiss R, Járay B, et al. (2017). Performance of a new HPV and biomarker assay in the management of hrHPV positive women: subanalysis of the ongoing multicenter TRACE clinical trial (*n* > 6,000) to evaluate POU4F3 methylation as a potential biomarker of cervical precancer and cancer. *Int J Cancer*. 140(5):1119–33. doi:10.1002/ijc.30534 PMID:27874187

Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PPL, Mustafa RA, et al. (2017). Cytology versus HPV testing for cervical cancer screening in the general population. *Cochrane Database Syst Rev*. 8:CD008587. doi:10.1002/14651858.CD008587.pub2 PMID:28796882

Kroenke K, Spitzer RL, Williams JB, Löwe B (2009). An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics*. 50(6):613–21. PMID:19996233

Kulasingam SL, Hughes JP, Kiviat NB, Mao C, Weiss NS, Kuypers JM, et al. (2002). Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity,

and frequency of referral. *JAMA*. 288(14):1749–57. doi:10.1001/jama.288.14.1749 PMID:12365959

Kwan TTC, Cheung ANY, Lo SST, Lee PWH, Tam KF, Chan KKL, et al. (2011). Psychological burden of testing positive for high-risk human papillomavirus on women with atypical cervical cytology: a prospective study. *Acta Obstet Gynecol Scand*. 90(5):445–51. doi:10.1111/j.1600-0412.2011.01092.x PMID:21306349

Labani S, Asthana S (2016). Age-specific performance of careHPV versus Papanicolaou and visual inspection of cervix with acetic acid testing in a primary cervical cancer screening. *J Epidemiol Community Health*. 70(1):72–7. doi:10.1136/jech-2015-205851 PMID:26248549

Lamin H, Eklund C, Elfström KM, Carlsten-Thor A, Hortlund M, Elfgren K, et al. (2017). Randomised healthcare policy evaluation of organised primary human papillomavirus screening of women aged 56–60. *BMJ Open*. 7(5):e014788. doi:10.1136/bmjopen-2016-014788 PMID:28566363

Leeflang MMG, Deeks JJ, Gatsonis C, Bossuyt PMM; Cochrane Diagnostic Test Accuracy Working Group (2008). Systematic reviews of diagnostic test accuracy. *Ann Intern Med*. 149(12):889–97. doi:10.7326/0003-4819-149-12-200812160-00008 PMID:19075208

Leinonen MK, Anttila A, Malila N, Dillner J, Forslund O, Nieminen P (2013). Type- and age-specific distribution of human papillomavirus in women attending cervical cancer screening in Finland. *Br J Cancer*. 109(11):2941–50. doi:10.1038/bjc.2013.647 PMID:24136148

Leinonen MK, Nieminen P, Lönnberg S, Malila N, Hakama M, Pokhrel A, et al. (2012). Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. *BMJ*. 345:e7789. doi:10.1136/bmj.e7789 PMID:23197596

Leinonen MK, Schee K, Jonassen CM, Lie AK, Nystrand CF, Rangberg A, et al. (2018). Safety and acceptability of human papillomavirus testing of self-collected specimens: a methodologic study of the impact of collection devices and HPV assays on sensitivity for cervical cancer and high-grade lesions. *J Clin Virol*. 99–100:22–30. doi:10.1016/j.jcv.2017.12.008 PMID:29289814

Li N, Shi JF, Franceschi S, Zhang WH, Dai M, Liu B, et al. (2009). Different cervical cancer screening approaches in a Chinese multicentre study. *Br J Cancer*. 100(3):532–7. doi:10.1038/sj.bjc.6604840 PMID:19127262

Longatto-Filho A, Naud P, Derchain SFM, Roteli-Martins C, Tatti S, Hammes LS, et al. (2012). Performance characteristics of Pap test, VIA, VILI, HR-HPV testing, cervicography, and colposcopy in diagnosis of significant cervical pathology. *Virchows Arch*. 460(6):577–85. doi:10.1007/s00428-012-1242-y PMID:22562132

Lorincz AT (1997). Methods of DNA hybridisation and their clinical applicability to human papillomavirus detection. In: Franco EL, Monsonego J, editors. New developments in cervical cancer screening and prevention. Oxford, UK: Blackwell; pp. 325–37.

Luo H, Du H, Belinson JL, Wu R (2019). Evaluation of alternately combining HPV viral load and 16/18 genotyping in secondary screening algorithms. *PLoS One*. 14(7):e0220200. doi:10.1371/journal.pone.0220200 PMID:31348794

Luyten A, Buttmann-Schweiger N, Luyten K, Mauritz C, Reinecke-Lüthge A, Pietralla M, et al. (2014). Early detection of CIN3 and cervical cancer during long-term follow-up using HPV/Pap smear co-testing and risk-adapted follow-up in a locally organised screening programme. *Int J Cancer*. 135(6):1408–16. doi:10.1002/ijc.28783 PMID:24519782

Machalek DA, Roberts JM, Garland SM, Thurloe J, Richards A, Chambers I, et al. (2019). Routine cervical screening by primary HPV testing: early findings in the renewed National Cervical Screening Program. *Med J Aust*. 211(3):113–9. doi:10.5694/mja2.50223 PMID:31168828

Maggino T, Sciarrone R, Murer B, Dei Rossi MR, Fedato C, Maran M, et al. (2016). Screening women for cervical cancer carcinoma with a HPV mRNA test: first results from the Venice pilot program. *Br J Cancer*. 115(5):525–32. doi:10.1038/bjc.2016.216 PMID:27490801

Mahmud SM, Sangwa-Lugoma G, Nasr SH, Kayembe PK, Tozin RR, Drouin P, et al. (2012). Comparison of human papillomavirus testing and cytology for cervical cancer screening in a primary health care setting in the Democratic Republic of the Congo. *Gynecol Oncol*. 124(2):286–91. doi:10.1016/j.ygyno.2011.10.031 PMID:22062546

Maissi E, Marteau TM, Hankins M, Moss S, Legood R, Gray A (2004). Psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: cross sectional questionnaire study. *BMJ*. 328(7451):1293. doi:10.1136/bmj.328.7451.1293 PMID:15166066

Maissi E, Marteau TM, Hankins M, Moss S, Legood R, Gray A (2005). The psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: 6-month follow-up. *Br J Cancer*. 92(6):990–4. doi:10.1038/sj.bjc.6602411 PMID:15785734

Malone C, Tiro JA, Buist DSM, Beatty T, Lin J, Kimbel K, et al. (2020). Reactions of women underscreened for cervical cancer who received unsolicited human papillomavirus self-sampling kits. *J Med Screen*. 27(3):146–56. doi:10.1177/0969141319885994 PMID:31744374

Mao C, Kulasingam SL, Whitham HK, Hawes SE, Lin J, Kiviat NB (2017). Clinician and patient acceptability of self-collected human papillomavirus testing for cervical cancer screening. *J Womens Health*

(Larchmt). 26(6):609–15. doi:10.1089/jwh.2016.5965 PMID:28332888

Markovic-Denic L, Djuric O, Maksimovic N, Popovac S, Kesic V (2018). Effects of human papillomavirus awareness and knowledge on psychological state of women referred to cervical cancer screening. *J Low Genit Tract Dis*. 22(3):178–83. doi:10.1097/LGT.0000000000000397 PMID:29672447

Marteau TM, Bekker H (1992). The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). *Br J Clin Psychol*. 31(3):301–6. doi:10.1111/j.2044-8260.1992.tb00997.x PMID:1393159

Mast TC, Zhu X, Demuro-Mercon C, Cummings HW, Sings HL, Ferris DG (2009). Development and psychometric properties of the HPV Impact Profile (HIP) to assess the psychosocial burden of HPV. *Curr Med Res Opin*. 25(11):2609–19. doi:10.1185/03007990903238786 PMID:19739938

Mayrand MH, Duarte-Franco E, Coutlée F, Rodrigues I, Walter SD, Ratnam S, et al.; CCCaST Study Group (2006). Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian Cervical Cancer Screening Trial (CCCaST). *Int J Cancer*. 119(3):615–23. doi:10.1002/ijc.21897 PMID:16572425

Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al.; Canadian Cervical Cancer Screening Trial Study Group (2007). Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med*. 357(16):1579–88. doi:10.1056/NEJMoa071430 PMID:17942871

Maza M, Melendez M, Masch R, Alfaro K, Chacon A, Gonzalez E, et al. (2018). Acceptability of self-sampling and human papillomavirus testing among non-attenders of cervical cancer screening programs in El Salvador. *Prev Med*. 114:149–55. doi:10.1016/j.ypmed.2018.06.017 PMID:29958860

Mbatha JN, Galappaththi-Arachchige HN, Mtshali A, Taylor M, Ndhlovu PD, Kjetland EF, et al. (2017). Self-sampling for human papillomavirus testing among rural young women of KwaZulu-Natal, South Africa. *BMC Res Notes*. 10(1):702. doi:10.1186/s13104-017-3045-3 PMID:29208043

McBride E, Marlow LAV, Forster AS, Ridout D, Kitchener H, Patnick J, et al. (2020). Anxiety and distress following receipt of results from routine HPV primary testing in cervical screening: the Psychological Impact of Primary Screening (PIPS) study. *Int J Cancer*. 146(8):2113–21. doi:10.1002/ijc.32540 PMID:31251820

McCaffery K, Waller J, Forrest S, Cadman L, Szarewski A, Wardle J (2004). Testing positive for human papillomavirus in routine cervical screening: examination

of psychosocial impact. *BJOG*. 111(12):1437–43. doi:10.1111/j.1471-0528.2004.00279.x PMID:15663132

McCaffery K, Waller J, Nazroo J, Wardle J (2006). Social and psychological impact of HPV testing in cervical screening: a qualitative study. *Sex Transm Infect*. 82(2):169–74. doi:10.1136/sti.2005.016436 PMID:16581749

McCaffery KJ, Irwig L, Turner R, Chan SF, Macaskill P, Lewicka M, et al. (2010). Psychosocial outcomes of three triage methods for the management of borderline abnormal cervical smears: an open randomised trial. *BMJ*. 340:b4491. doi:10.1136/bmj.b4491 PMID:20179125

Meijer CJLM, Berkhof J, Castle PE, Hesselink AT, Franco EL, Ronco G, et al. (2009). Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. *Int J Cancer*. 124(3):516–20. doi:10.1002/ijc.24010 PMID:18973271

Melnikow J, Henderson JT, Burda BU, Senger CA, Durbin S, Weyrich MS (2018). Screening for cervical cancer with high-risk human papillomavirus testing: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 320(7):687–705. doi:10.1001/jama.2018.10400 PMID:30140883

Mesher D, Szarewski A, Cadman L, Cubie H, Kitchener H, Luesley D, et al. (2010). Long-term follow-up of cervical disease in women screened by cytology and HPV testing: results from the HART study. *Br J Cancer*. 102(9):1405–10. doi:10.1038/sj.bjc.6605619 PMID:20354519

Mittal S, Mandal R, Banerjee D, Das P, Ghosh I, Panda C, et al. (2016). HPV detection-based cervical cancer screening program in low-resource setting: lessons learnt from a community-based demonstration project in India. *Cancer Causes Control*. 27(3):351–8. doi:10.1007/s10552-015-0708-z PMID:26712612

Moberg M, Gustavsson I, Gyllensten U (2004). Type-specific associations of human papillomavirus load with risk of developing cervical carcinoma *in situ*. *Int J Cancer*. 112(5):854–9. doi:10.1002/ijc.20480 PMID:15386375

Modibbo F, Iregbu KC, Okuma J, Leeman A, Kasius A, de Koning M, et al. (2017). Randomized trial evaluating self-sampling for HPV DNA based tests for cervical cancer screening in Nigeria. *Infect Agent Cancer*. 12(1):11. doi:10.1186/s13027-017-0123-z PMID:28184239

Monsonego J, Hudgens MG, Zerat L, Zerat JC, Syrjänen K, Halfon P, et al. (2011). Evaluation of oncogenic human papillomavirus RNA and DNA tests with liquid-based cytology in primary cervical cancer screening: the FASE study. *Int J Cancer*. 129(3):691–701. doi:10.1002/ijc.25726 PMID:20941740

Moy LM, Zhao FH, Li LY, Ma JF, Zhang QM, Chen F, et al. (2010). Human papillomavirus testing and cervical cytology in primary screening for cervical cancer among women in rural China: comparison of sensitivity, specificity, and frequency of referral. *Int J Cancer*. 127(3):646–56. doi:10.1002/ijc.25071 PMID:19960441

Muangto T, Chanthasenanont A, Lertvutivivat S, Nanthakomon T, Pongrojpaw D, Bhamarapravatana K, et al. (2016). Experience of combined liquid based cervical cytology and high-risk HPV mRNA for cervical cancer screening in Thammasat University Hospital. *Asian Pac J Cancer Prev*. 17(9):4409–13. PMID:27797253

Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. (2016). Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. *Int J Gynaecol Obstet*. 132(3):259–65. doi:10.1016/j.ijgo.2015.07.024 PMID:26851054

Muwonge R, Wesley RS, Nene BM, Shastri SS, Jayant K, Malvi SG, et al. (2014). Evaluation of cytology and visual triage of human papillomavirus-positive women in cervical cancer prevention in India. *Int J Cancer*. 134(12):2902–9. doi:10.1002/ijc.28627 PMID:24272364

Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al. (2007). Human papillomavirus and Papanicolaou tests to screen for cervical cancer. [Erratum in: N Engl J Med. 2008 359(15):1637. Johansson, Bo (added)] *N Engl J Med*. 357(16):1589–97. doi:10.1056/NEJMoa073204 PMID:17942872

Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al. (2009). Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. *J Natl Cancer Inst*. 101(2):88–99. doi:10.1093/jnci/djn444 PMID:19141778

Nelson EJ, Maynard BR, Loux T, Fatla J, Gordon R, Arnold LD (2017). The acceptability of self-sampled screening for HPV DNA: a systematic review and meta-analysis. *Sex Transm Infect*. 93(1):56–61. doi:10.1136/sextrans-2016-052609 PMID:28100761

Nieves L, Enerson CL, Belinson S, Brainard J, Chiesa-Vottero A, Nagore N, et al. (2013). Primary cervical cancer screening and triage using an mRNA human papillomavirus assay and visual inspection. *Int J Gynecol Cancer*. 23(3):513–8. doi:10.1097/IGC.0b013e318280f3bc PMID:23334437

O'Connor M, Costello L, Murphy J, Prendiville W, Martin CM, O'Leary JJ, et al.; Irish Screening Research Consortium (CERVIVA) (2014). 'I don't care whether it's HPV or ABC, I just want to know if I have cancer.' Factors influencing women's emotional responses to undergoing human papillomavirus testing in routine management in cervical screening: a qualitative study. *BJOG*. 121(11):1421–9. doi:10.1111/1471-0528.12741 PMID:24690225

Ogilvie GS, Krajden M, van Niekerk D, Smith LW, Cook D, Ceballos K, et al. (2017). HPV For Cervical Cancer Screening (HPV FOCAL): complete round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer. *Int J Cancer*. 140(2):440–8. doi:10.1002/ijc.30454 PMID:27685757

Ogilvie GS, van Niekerk D, Krajden M, Smith LW, Cook D, Gondara L, et al. (2018). Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA*. 320(1):43–52. doi:10.1001/jama.2018.7464 PMID:29971397

Oketch SY, Kwena Z, Choi Y, Adewumi K, Moghadassi M, Bukusi EA, et al. (2019). Perspectives of women participating in a cervical cancer screening campaign with community-based HPV self-sampling in rural western Kenya: a qualitative study. *BMC Women's Health*. 19(1):75. doi:10.1186/s12905-019-0778-2 PMID:31196175

Ovestad IT, Vennestrøm U, Andersen L, Gudlaugsson E, Munk AC, Malpica A, et al. (2011). Comparison of different commercial methods for HPV detection in follow-up cytology after ASCUS/LSIL, prediction of CIN2–3 in follow up biopsies and spontaneous regression of CIN2–3. *Gynecol Oncol*. 123(2):278–83. doi:10.1016/j.ygyno.2011.07.024 PMID:21835440

Pan Q, Belinson JL, Li L, Pretorius RG, Qiao YL, Zhang WH, et al. (2003). A thin-layer, liquid-based Pap test for mass screening in an area of China with a high incidence of cervical carcinoma. A cross-sectional, comparative study. *Acta Cytol*. 47(1):45–50. doi:10.1159/000326474 PMID:12585030

Pan QJ, Hu SY, Guo HQ, Zhang WH, Zhang X, Chen W, et al. (2014). Liquid-based cytology and human papillomavirus testing: a pooled analysis using the data from 13 population-based cervical cancer screening studies from China. *Gynecol Oncol*. 133(2):172–9. doi:10.1016/j.ygyno.2014.03.008 PMID:24631450

Papa D, Moore Simas TA, Reynolds M, Melnitsky H (2009). Assessing the role of education in women's knowledge and acceptance of adjunct high-risk human papillomavirus testing for cervical cancer screening. *J Low Genit Tract Dis*. 13(2):66–71. doi:10.1097/LGT.0b013e31818a53f0 PMID:19387125

Pasquale L, Giorgi Rossi P, Carozzi F, Pedretti C, Ruggeri C, Scalvinoni V, et al. (2015). Cervical cancer screening with HPV testing in the Valcamonica (Italy) screening programme. *J Med Screen*. 22(1):38–48. doi:10.1177/0969141314561707 PMID:25431452

Passamonti B, Gustinucci D, Giorgi Rossi P, Cesarini E, Bulletti S, Carlani A, et al. (2017). Cervical human papilloma virus (HPV) DNA primary screening test: results of a population-based screening programme in central Italy. *J Med Screen*. 24(3):153–62. doi:10.1177/0969141316663580 PMID:27614992

Patel H, Moss EL, Sherman SM (2018). HPV primary cervical screening in England: women's awareness and attitudes. *Psychooncology*. 27(6):1559–64. doi:10.1002/pon.4694 PMID:29521462

Petry KU, Menton S, Menton M, van Loenen-Frosch F, de Carvalho Gomes H, Holz B, et al. (2003). Inclusion of HPV testing in routine cervical cancer screening for women above 29 years in Germany: results for 8466 patients. *Br J Cancer*. 88(10):1570–7. doi:10.1038/sj.bjc.6600918 PMID:12771924

Poljak M, Oštrbenk Valenčak A, Gimpelj Domjanič G, Xu L, Arbyn M (2020). Commercially available molecular tests for human papillomaviruses: a global overview. *Clin Microbiol Infect*. 26(9):1144–50. doi:10.1016/j.cmi.2020.03.033 PMID:32247892

Polman NJ, de Haan Y, Veldhuijzen NJ, Heideman DAM, de Vet HCW, Meijer CJLM, et al. (2019c). Experience with HPV self-sampling and clinician-based sampling in women attending routine cervical screening in the Netherlands. *Prev Med*. 125:5–11. doi:10.1016/j.ypmed.2019.04.025 PMID:31054907

Polman NJ, Ebisch RMF, Heideman DAM, Melchers WJG, Bekkers RLM, Molijn AC, et al. (2019b). Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial. *Lancet Oncol*. 20(2):229–38. doi:10.1016/S1470-2045(18)30763-0 PMID:30658933

Polman NJ, Veldhuijzen NJ, Heideman DAM, Snijders PJF, Meijer CJLM, Berkhof J (2017). HPV-positive women with normal cytology remain at increased risk of CIN3 after a negative repeat HPV test. *Br J Cancer*. 117(10):1557–61. doi:10.1038/bjc.2017.309 PMID:28881359

Polman NJ, Veldhuijzen NJ, Heideman DAM, Snijders PJF, Meijer CJLM, Berkhof J (2019a). Management of HPV-positive women in cervical screening using results from two consecutive screening rounds. *Int J Cancer*. 144(9):2339–46. doi:10.1002/ijc.32004 PMID:30565673

Qiao YL, Jeronimo J, Zhao FH, Schweizer J, Chen W, Valdez M, et al. (2014). Lower cost strategies for triage of human papillomavirus DNA-positive women. *Int J Cancer*. 134(12):2891–901. doi:10.1002/ijc.28616 PMID:24248915

Rebolj M, Bonde J, Ejegod D, Preisler S, Rygaard C, Lynge E (2015). A daunting challenge: human papillomavirus assays and cytology in primary cervical screening of women below age 30 years. *Eur J Cancer*. 51(11):1456–66. doi:10.1016/j.ejca.2015.04.012 PMID:25979832

Rebolj M, Rimmer J, Denton K, Tidy J, Mathews C, Ellis K, et al. (2019). Primary cervical screening with high risk human papillomavirus testing: observational study. *BMJ*. 364:l240. doi:10.1136/bmj.l240 PMID:30728133

Rezhake R, Hu SY, Zhao S, Xu XQ, Zhao XL, Zhang L, et al. (2018). Eight-type human papillomavirus E6/E7 oncoprotein detection as a novel and promising triage strategy for managing HPV-positive women. *Int J Cancer*. 144(1):34–42. doi:10.1002/ijc.31633 PMID:29943809

Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NWJ, Heideman DAM, et al. (2012a). Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *Lancet Oncol*. 13(1):78–88. doi:10.1016/S1470-2045(11)70296-0 PMID:22177579

Rijkaart DC, Berkhof J, van Kemenade FJ, Coupe VMH, Rozendaal L, Heideman DAM, et al. (2012b). HPV DNA testing in population-based cervical screening (VUSA-Screen study): results and implications. *Br J Cancer*. 106(5):975–81. doi:10.1038/bjc.2011.581 PMID:22251922

Rijkaart DC, Berkhof J, van Kemenade FJ, Coupe VM, Hesselink AT, Rozendaal L, et al. (2012c). Evaluation of 14 triage strategies for HPV DNA-positive women in population-based cervical screening. *Int J Cancer*. 130(3):602–10. doi:10.1002/ijc.26056 PMID:21400507

Ronco G, Brezzi S, Carozzi F, Dalla Palma P, Giorgi-Rossi P, Minucci D, et al.; NTCC study group (2007a). The New Technologies for Cervical Cancer Screening randomised controlled trial. An overview of results during the first phase of recruitment. *Gynecol Oncol*. 107(Suppl 1):S230–2. doi:10.1016/j.ygyno.2007.07.021 PMID:17822751

Ronco G, Cuzick J, Segnan N, Brezzi S, Carozzi F, Folicaldi S, et al.; NTCC working group (2007b). HPV triage for low grade (L-SIL) cytology is appropriate for women over 35 in mass cervical cancer screening using liquid based cytology. *Eur J Cancer*. 43(3):476–80. doi:10.1016/j.ejca.2006.11.013 PMID:17223540

Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJF, Arbyn M, et al.; International HPV screening working group (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 383(9916):524–32. doi:10.1016/S0140-6736(13)62218-7 PMID:24192252

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al.; New Technologies for Cervical Cancer screening (NTCC) Working Group (2010). Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol*. 11(3):249–57. doi:10.1016/S1470-2045(09)70360-2 PMID:20089449

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al.; New Technologies for Cervical Cancer Screening Working Group (2008). Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. *J Natl Cancer Inst*. 100(7):492–501. doi:10.1093/jnci/djn065 PMID:18364502

Ronco G, Giorgi-Rossi P, Carozzi F, Dalla Palma P, Del Mistro A, De Marco L, et al.; New Technologies for Cervical Cancer Screening Working Group (2006a). Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. *Lancet Oncol*. 7(7):547–55. doi:10.1016/S1470-2045(06)70731-8 PMID:16814206

Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, et al.; New Technologies for Cervical Cancer Working Group (2006b). Human papillomavirus testing and liquid-based cytology: results at recruitment from the New Technologies for Cervical Cancer randomized controlled trial. *J Natl Cancer Inst*. 98(11):765–74. doi:10.1093/jnci/djj209 PMID:16757701

Salmerón J, Lazcano-Ponce E, Lorincz A, Hernández M, Hernández P, Leyva A, et al. (2003). Comparison of HPV-based assays with Papanicolaou smears for cervical cancer screening in Morelos State, Mexico. *Cancer Causes Control*. 14(6):505–12. doi:10.1023/A:1024806707399 PMID:12948281

Sangrajrang S, Laowahutanont P, Wongsena M, Muwonge R, Karalak A, Imsamran W, et al. (2017). Comparative accuracy of Pap smear and HPV screening in Ubon Ratchathani in Thailand. *Papillomavirus Res*. 3:30–5. doi:10.1016/j.pvr.2016.12.004 PMID:28720454

Sankaranarayanan R, Chatterji R, Shastri SS, Wesley RS, Basu P, Mahe C, et al. (2004). Accuracy of human papillomavirus testing in primary screening of cervical neoplasia: results from a multicenter study in India. *Int J Cancer*. 112(2):341–7. doi:10.1002/ijc.20396 PMID:15352050

Sankaranarayanan R, Nene BM, Dinshaw KA, Mahe C, Jayant K, Shastri SS, et al.; Osmanabad District Cervical Screening Study Group (2005). A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer*. 116(4):617–23. doi:10.1002/ijc.21050 PMID:15818610

Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. (2009). HPV screening for cervical cancer in rural India. *N Engl J Med*. 360(14):1385–94. doi:10.1056/NEJMoa0808516 PMID:19339719

Sargent A, Fletcher S, Bray K, Kitchener HC, Crosbie EJ (2019). Cross-sectional study of HPV testing in self-sampled urine and comparison with matched vaginal and cervical samples in women attending colposcopy for

the management of abnormal cervical screening. *BMJ Open*. 9(4):e025388. doi:10.1136/bmjopen-2018-025388 PMID:31036707

Sarian LO, Derchain S, Shabalova I, Tatti S, Naud P, Longatto-Filho A, et al.; members of the Latin American Screening Study (LAMS) and the New Independent States of the Former Soviet Union (NIS) groups (2010). Optional screening strategies for cervical cancer using standalone tests and their combinations among low- and medium-income populations in Latin America and Eastern Europe. *J Med Screen*. 17(4):195–203. doi:10.1258/jms.2010.010016 PMID:21258130

Schiffman M, Kinney WK, Cheung LC, Gage JC, Fetterman B, Poitras NE, et al. (2018). Relative performance of HPV and cytology components of cotesting in cervical screening. *J Natl Cancer Inst*. 110(5):501–8. doi:10.1093/jnci/djx225 PMID:29145648

Senkomago V, Ting J, Kwatampora J, Gukare H, Mugo N, Kimani J, et al. (2018). High-risk HPV-RNA screening of physician- and self-collected specimens for detection of cervical lesions among female sex workers in Nairobi, Kenya. *Int J Gynaecol Obstet*. 143(2):217–24. doi:10.1002/ijgo.12628 PMID:30047987

Sherman ME, Schiffman M, Cox JT; Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study Group (2002). Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). *J Natl Cancer Inst*. 94(2):102–7. doi:10.1093/jnci/94.2.102 PMID:11792748

Snijders PJF, van den Brule AJC, Meijer CJLM (2003). The clinical relevance of human papillomavirus testing: relationship between analytical and clinical sensitivity. *J Pathol*. 201(1):1–6. doi:10.1002/path.1433 PMID:12950011

Stoler MH, Wright TC Jr, Cuzick J, Dockter J, Reid JL, Getman D, et al. (2013). APTIMA HPV assay performance in women with atypical squamous cells of undetermined significance cytology results. *Am J Obstet Gynecol*. 208(2):144.e1–8. doi:10.1016/j.ajog.2012.12.003 PMID:23220509

Sultana F, Mullins R, English DR, Simpson JA, Drennan KT, Heley S, et al. (2015). Women's experience with home-based self-sampling for human papillomavirus testing. *BMC Cancer*. 15(1):849. doi:10.1186/s12885-015-1804-x PMID:26536865

Tang NS, Tang ML, Chan ISF (2003). On tests of equivalence via non-unity relative risk for matched-pair design. *Stat Med*. 22(8):1217–33. doi:10.1002/sim.1213 PMID:12687652

Terrazas S, Ibáñez C, Lagos M, Poggi H, Brañes J, Barriga MI, et al. (2015). Human papillomavirus testing in cervical cancer screening at a public health service of Santiago, Chile. [in Spanish] *Rev Med Chil*. 143(1):56–62. doi:10.4067/S0034-98872015000100007 PMID:25860269

Thomsen LT, Kjær SK, Munk C, Frederiksen K, Ørnskov D, Waldstrøm M (2020). Clinical performance of human papillomavirus (HPV) testing versus cytology for cervical cancer screening: results of a large Danish implementation study. *Clin Epidemiol*. 12:203–13. doi:10.2147/CLEP.S243546 PMID:32110112

Tian Q, Li Y, Wang F, Li Y, Xu J, Shen Y, et al. (2014). MicroRNA detection in cervical exfoliated cells as a triage for human papillomavirus-positive women. *J Natl Cancer Inst*. 106(9):dju241. doi:10.1093/jnci/dju241 PMID:25190727

Torres-Ibarra L, Cuzick J, Lorincz AT, Spiegelman D, Lazcano-Ponce E, Franco EL, et al.; FRIDA Study Group (2019). Comparison of HPV-16 and HPV-18 genotyping and cytological testing as triage testing within human papillomavirus-based screening in Mexico. *JAMA Netw Open*. 2(11):e1915781. doi:10.1001/jamanetworkopen.2019.15781 PMID:31747033

Tshomo U, Franceschi S, Tshokey T, Tobgay T, Baussano I, Tenet V, et al. (2017). Evaluation of cytology versus human papillomavirus-based cervical cancer screening algorithms in Bhutan. *Oncotarget*. 8(42):72438–46. doi:10.18632/oncotarget.19783 PMID:29069800

Veijalainen O, Kares S, Kujala P, Vuento R, Osuala V, Tirkkonen M, et al. (2019). Implementation of HPV-based cervical cancer screening in an organised regional screening programme: 3 years of experience. *Cytopathology*. 30(2):150–6. doi:10.1111/cyt.12652 PMID:30421573

Veldhuijzen NJ, Polman NJ, Snijders PJF, Meijer CJLM, Berkhof J (2017). Stratifying HPV-positive women for CIN3+ risk after one and two rounds of HPV-based screening. *Int J Cancer*. 141(8):1551–60. doi:10.1002/ijc.30865 PMID:28670823

Verdoodt F, Szarewski A, Halfon P, Cuschieri K, Arbyn M (2013). Triage of women with minor abnormal cervical cytology: meta-analysis of the accuracy of an assay targeting messenger ribonucleic acid of 5 high-risk human papillomavirus types. *Cancer Cytopathol*. 121(12):675–87. doi:10.1002/cncy.21325 PMID:23881840

von Karsa L, Arbyn M, De Vuyst H, Dillner J, Dillner L, Franceschi S, et al. (2015). European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. *Papillomavirus Res*. 1:22–31. doi:10.1016/j.pvr.2015.06.006

Waller J, Marlow LAV, Wardle J (2007). The association between knowledge of HPV and feelings of stigma, shame and anxiety. *Sex Transm Infect*. 83(2):155–9. doi:10.1136/sti.2006.023333 PMID:17098767

Wang MZ, Feng RM, Wang S, Duan XZ, Li D, Zhang X, et al. (2019). Clinical performance of human papillomavirus testing and visual inspection with acetic acid in

primary, combination, and sequential cervical cancer screening in China. *Sex Transm Dis.* 46(8):540–7. doi:10.1097/OLQ.0000000000001026 PMID:31295223

Wang M, Hu S, Zhao S, Zhang W, Pan Q, Zhang X, et al. (2017). Accuracy of triage strategies for human papillomavirus DNA-positive women in low-resource settings: a cross-sectional study in China. *Chin J Cancer Res.* 29(6):496–509. doi:10.21147/j.issn.1000-9604.2017.06.04 PMID:29353972

Wang SM, Shi JF, Kang DJ, Song P, Qiao YL; Chinese HPV Study Group (2011). Impact of human papillomavirus-related lesions on quality of life: a multicenter hospital-based study of women in mainland China. *Int J Gynecol Cancer.* 21(1):182–8. doi:10.1097/IGC.0b013e3181ffbed8 PMID:21330842

Wardle J, Pernet A, Stephens D (1995). Psychological consequences of positive results in cervical cancer screening. *Psychol Health.* 10(3):185–94. doi:10.1080/08870449508401948

Wentzensen N, Fetterman B, Castle PE, Schiffman M, Wood SN, Stiemerling E, et al. (2015). p16/Ki-67 dual stain cytology for detection of cervical precancer in HPV-positive women. *J Natl Cancer Inst.* 107(12):djv257. doi:10.1093/jnci/djv257 PMID:26376685

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al.; QUADAS-2 Group (2011). QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 155(8):529–36. doi:10.7326/0003-4819-155-8-201110180-00009 PMID:22007046

WHO (2010). Human papillomavirus laboratory manual. 1st ed. Geneva, Switzerland: World Health Organization, Department of Immunization, Vaccines and Biologicals. Available from: https://apps.who.int/iris/handle/10665/70505.

WHO (2019). Protocol for the performance evaluation of qualitative HPV nucleic acid based assays for WHO prequalification assessment. Geneva, Switzerland: World Health Organization.

WHO (2020a). WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/331698.

WHO (2020b). Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/336583.

Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL (2015). Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. *Gynecol Oncol.* 136(2):189–97. doi:10.1016/j.ygyno.2014.11.076 PMID:25579108

Wu R, Belinson SE, Du H, Na W, Qu X, Wu R, et al. (2010). Human papillomavirus messenger RNA assay for cervical cancer screening: the Shenzhen Cervical Cancer Screening Trial I. *Int J Gynecol Cancer.* 20(8):1411–4. PMID:21051986

Wu Q, Zhao X, Fu Y, Wang X, Zhang X, Tian X, et al. (2017). A cross-sectional study on HPV testing with type 16/18 genotyping for cervical cancer screening in 11,064 Chinese women. *Cancer Med.* 6(5):1091–101. doi:10.1002/cam4.1060 PMID:28378404

Zhang L, Xu XQ, Hu SY, Chen F, Zhang X, Pan QJ, et al. (2018). Durability of clinical performance afforded by self-collected HPV testing: a 15-year cohort study in China. *Gynecol Oncol.* 151(2):221–8. doi:10.1016/j.ygyno.2018.09.012 PMID:30269870

Zhao FH, Jeronimo J, Qiao YL, Schweizer J, Chen W, Valdez M, et al. (2013). An evaluation of novel, lower-cost molecular screening tests for human papillomavirus in rural China. *Cancer Prev Res (Phila).* 6(9):938–48. doi:10.1158/1940-6207.CAPR-13-0091 PMID:23878179

Zhao FH, Lin MJ, Chen F, Hu SY, Zhang R, Belinson JL, et al.; Cervical Cancer Screening Group in China (2010). Performance of high-risk human papillomavirus DNA testing as a primary screen for cervical cancer: a pooled analysis of individual patient data from 17 population-based studies from China. *Lancet Oncol.* 11(12):1160–71. doi:10.1016/S1470-2045(10)70256-4 PMID:21075054

Zhao YQ, Dai Y, Dang L, Kong LH, Zhang Y, Feng RM, et al. (2018). Real-world research on cervical cancer screening program and effect evaluation for Chinese population. [in Chinese] *Chin J Oncol.* 40(10):764–71. doi:10.3760/cma.j.issn.0253-3766.2018.10.008 PMID:30392341

Zhao J, Du H, Belinson JL, Qu X, Zhang W, Mei J, et al. (2016b). Evaluation of the Cervista HPV A9 group in screening patients for cervical cancer. *J Med Screen.* 23(1):38–43. doi:10.1177/0969141315604863 PMID:26466824

Zhao FH, Hu SY, Zhang Q, Zhang X, Pan QJ, Zhang WH, et al. (2016a). Risk assessment to guide cervical screening strategies in a large Chinese population. *Int J Cancer.* 138(11):2639–47. doi:10.1002/ijc.30012 PMID:26800481

Zigmond AS, Snaith RP (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand.* 67(6):361–70. doi:10.1111/j.1600-0447.1983.tb09716.x PMID:6880820

Zorzi M, Del Mistro A, Giorgi Rossi P, Laurino L, Battagello J, Lorio M, et al. (2020). Risk of CIN2 or more severe lesions after negative HPV-mRNA E6/E7 overexpression assay and after negative HPV-DNA test: concurrent cohorts with a 5-year follow-up. *Int J Cancer.* 146(11):3114–23. doi:10.1002/ijc.32695 PMID:31583683

Zorzi M, Frayle H, Rizzi M, Fedato C, Rugge M, Penon MG, et al.; Veneto HPV-screening Working Group (2017). A 3-year interval is too short for re-screening women testing negative for human papillomavirus: a population-based cohort study. *BJOG.* 124(10):1585–93. doi:10.1111/1471-0528.14575 PMID:28120382

zur Hausen H (2002). Papillomaviruses and cancer: from basic studies to clinical application. *Nat Rev Cancer.* 2(5):342–50. doi:10.1038/nrc798 PMID:12044010

4.5 Colposcopy

A colposcope is a low-magnification, light-illuminated, stereoscopic, binocular field microscope. It is used for visual examination of the lower genital tract, including the cervix. Colposcopic examination facilitates the identification of the TZ (see Fig. 1.18 in Section 1.2.5), which is where most cervical cancers originate, and the characterization and localization of intraepithelial lesions in the lower genital tract to guide biopsies, where necessary, for confirmation of disease status.

In the 20th century, colposcopy was used in many countries as part of a standard gynaecological examination (van Niekerk et al., 1998). It is still used as a primary screening tool, together with cytology, by some clinicians in a few countries in Europe and Latin America. The rationale for this combined testing approach is that the use of the colposcope to guide cytology sample collection may decrease the false-negative and false-positive rates associated with blind sampling, and may also reduce the need for women to be recalled for repeat cytology (van Niekerk et al., 1998). However, there is no agreement about whether colposcopic impression improves the quality of cytology testing (Hilgarth & Menton, 1996; Schulmeyer et al., 2020). Moreover, it has been shown that colposcopy does not perform well for primary screening (Leeson et al., 2014; AEPCC, 2018). In contrast, there is wide consensus that colposcopy is the cornerstone of management of women with a positive Pap test result or symptomatic women. Table 4.33 shows the indications for performing colposcopy.

4.5.1 Technical description of a colposcopic examination

In 1925, Hinselmann (Hinselmann, 1925; Jordan, 1985) designed the colposcope and described how to enhance the colposcopic view

of the cervical epithelium to recognize cervical cancer and precancer by staining the cervix with acetic acid (Soutter, 1993). In 1929, Schiller introduced the use of iodine and showed that areas of the cervix harbouring early cervical cancer did not stain with iodine, in contrast to the dark staining of normal squamous epithelium of the ectocervix (Schiller, 1933; Colgan & Lickrish, 1990; Bappa & Yakasai, 2013). Initially colposcopy was used for primary screening, but during the 1960s studies showed that colposcopy enabled the more accurate localization of suspected lesions after cytology testing, which made it possible to more accurately select biopsy sites and reduced the need for diagnostic conization (Beller & Khatamee, 1966; Ruiz Moreno, 2010). These studies established the basis for the current use of colposcopy within the cytology–colposcopy–histology sequence.

When colposcopy is performed in a competent and quality-assured service, it is a comprehensive examination and provides information that is crucial for optimal clinical management. Colposcopy has important advantages, particularly for women with endocervical or glandular disease, very large lesions, or suspicion of invasion or microinvasive disease, and for lesions that are present during pregnancy or for residual or recurrent disease after treatment.

A colposcopic examination aims to:

- determine the adequacy of the examination;
- determine the site, size, and type of the TZ;
- recognize intraepithelial abnormality where present;
- identify the most accurate biopsy site for sampling; and
- facilitate precise treatment.

Table 4.33 Indications for performing colposcopy

Abnormal results in screening tests (cytology or HPV test) suggesting an increased risk of cervical intraepithelial neoplasia
Follow-up of patients with an intraepithelial lesion before or after treatment
Excisional treatment of premalignant lesions of the cervix, as an auxiliary method to guide the procedure
Presence of clinically apparent leukoplakia or any suspicious-looking or abnormal-looking cervix in the gynaecological examination
Presence of symptoms suggesting cervical cancer (unusual bleeding, abnormal vaginal discharge, etc.)

HPV, human papillomavirus.
Compiled by the Working Group.

(a)   The colposcope

A colposcope has the following features (for more details, see Prendiville & Sankaranarayanan, 2017):

- A support for the colposcope head, which is the working part. This support can be either a simple vertical stand that is positioned between the operator's legs or an adjustable horizontal arm connected to a weighted stand that is positioned lateral to the patient and the operator and is attached to the colposcope head by a universal joint.

- Binocular view, so that depth of field may be appreciated. (Improving image-capture systems may reduce the disadvantages of monocular devices.) Depth of field is crucial for accurate assessment of the TZ or when performing excision of the TZ.

- Variable magnification, either stepwise or using a zoom facility.

- White light from a halogen light or, preferably, a light-emitting diode (LED) lamp.

- A green or blue filter, or green or blue light.

- Image capture.

- Facility to adjust the eyepieces to the operator's interpupillary distance.

- Fine focus adjustment.

(b)   Performing a colposcopic examination

For a colposcopic examination to be performed competently, the following are required: a well-trained colposcopist, a well-equipped examination room (see Prendiville & Sankaranarayanan, 2017), and a skilled attendant.

The examiner inserts a speculum to expose the cervix and position it in a plane perpendicular to the colposcopic line of vision. The colposcope enables the examination of the whole lower genital tract, including the cervix, vagina, and vulva. The examiner first assesses whether the examination can be performed adequately (Bornstein et al., 2012). If so, the next step is to examine the cervix at low-power magnification and gently cleanse it with saline. The hormonal status and degree of inflammation are assessed. Once adequacy has been confirmed, the TZ is examined at low-power magnification, perhaps with a green filter, before 3% to 5% acetic acid is applied. Use of an endocervical forceps (preferably the Desjardins or Kurihara forceps) is often needed to achieve full visualization of the upper limit of the TZ, particularly in postmenopausal women. Examination of the TZ is performed at both low-power and high-power magnification. Documentation of the examination findings completes the colposcopy, and a management plan may be discussed with the patient.

Table 4.34 Modifications in colposcopic terminology over time

Terminology (name, year)	Normal findings	Abnormal findings	Other terms	Reference
Hinselmann, 1933	Thick leukoplakia	Mosaic leukoplakia	Cervico-uterine ectopy	ASCCP guidelines, Mayeaux & Cox (2013)
Coppleson, 1960	Grade I: not suspicious, white semi-transparent epithelium, flat, with indistinct borders	Grade II: suspicious white epithelium Grade III: opaque epithelium with very suspicious defined borders	Transformation zone	Reid & Campion (1989)
IFCPC Graz, 1975	Normal colposcopy	Atypical transformation zone	Colposcopy not satisfactory Miscellaneous	Stafl (1976)
Reid score, 1985	Category 1: benign, minor dysplasia	Category 2: intermediate Category 3: suspicious	Four criteria: border, colour, vessels, iodine uptake	Reid & Campion (1989)
IFCPC Rome, 1990	Normal colposcopy Cylindrical epithelium: ectopy	Abnormal colposcopy within or outside the transformation zone Fine or coarse mosaic or punctation	Miscellaneous not acetowhite	Stafl & Wilbanks (1991)
IFCPC Barcelona, 2002	Type 1, 2, 3 transformation zone	Minor or major changes Suggestive of low-grade or high-grade lesion	Colposcopy suggestive of invasive cancer	Walker et al. (2003)
IFCPC Rio de Janeiro, 2011	Includes metaplasia and deciduosis	Grade 1 or grade 2 changes Location of lesion, number of cervical quadrants the lesion covers New signs: inner border sign and ridge sign	Includes description of vaginal lesions Incorporates types of excision	Bornstein et al. (2012)

ASCCP, American Society for Colposcopy and Cervical Pathology; IFCPC, International Federation of Cervical Pathology and Colposcopy.

(c) Colposcopic terminology and correlation with histological diagnosis

Different classifications have been used throughout the 90-year history of colposcopy (AEPCC, 2018). Table 4.34 shows the most relevant and clinically used global colposcopic classifications and the modifications that have been introduced over time. Currently, the classification that is most commonly used in health-care practice worldwide is that adopted unanimously by the International Federation of Cervical Pathology and Colposcopy (IFCPC). The most recent IFCPC terminology, prepared in 2011 (Bornstein et al., 2012), is summarized in Table 4.35. However, in this section, results from scientific publications are presented according to the terminology as reported originally, wherever possible.

Substantial information is available on the correlation between the categorization of lesions using the IFCPC classification and the histological diagnosis. Some studies have reported a good correlation between the colposcopic impression and the final diagnosis (Ferris & Litaker, 2005). Some particular findings (such as coarse punctation, coarse mosaic or dense acetowhitening, inner border sign, and ridge sign) have been shown to have a good predictive accuracy for HSIL+/CIN2+ (Vercellino et al., 2013; Beyer et al., 2017; Li et al., 2017), although the sensitivity of colposcopic impression for detection of HSIL+/CIN2+ ranged from 20% to 100%

Table 4.35 2011 IFCPC colposcopic terminology of the cervix

Section	Pattern	
General assessment	Adequate or inadequate; if inadequate, for what reason (e.g. cervix obscured by inflammation, bleeding, scar) Squamocolumnar junction visibility: completely visible, partially visible, not visible Transformation zone types 1, 2, 3	
Normal colposcopic findings	Original squamous epithelium: mature, atrophic Columnar epithelium; ectopy or ectropion Metaplastic squamous epithelium; nabothian cysts; crypt (gland) openings Deciduosis in pregnancy	
Abnormal colposcopic findings	*General principles* Location of the lesion: • Inside or outside the transformation zone • By the "clock position"	Size of the lesion: • Number of cervical quadrants the lesion covers • Size of the lesion as a percentage of the cervix
	Grade 1 (minor) • Fine mosaic; fine punctation • Thin acetowhite epithelium • Irregular, geographical border	*Grade 2 (major)* • Sharp border; inner border sign; ridge sign • Dense acetowhite epithelium • Coarse mosaic; coarse punctation • Rapid appearance of acetowhitening • Cuffed crypt (gland) openings
	Non-specific • Leukoplakia (keratosis, hyperkeratosis); erosion • Lugol's staining (Schiller test): stained or non-stained	
Suspicious for invasion	Atypical vessels Additional signs: • Fragile vessels • Irregular surface • Exophytic lesion • Necrosis • Ulceration (necrotic) • Tumour or gross neoplasm	
Miscellaneous findings	Congenital transformation zone Condyloma Polyp (ectocervical or endocervical) Inflammation	Stenosis Congenital anomaly Post-treatment consequence Endometriosis
Excision treatment types	Excision types 1, 2, 3	
Excision specimen dimensions	Length: the distance from the distal or external margin to the proximal or internal margin Thickness: the distance from the stromal margin to the surface of the excised specimen Circumference (optional): the perimeter of the excised specimen	

IFCPC, International Federation of Cervical Pathology and Colposcopy.
From Bornstein et al. (2012).

and the specificity from 96% to 99%. However, some authors have suggested that the degree of concordance depends mainly on the training and the experience or expertise of the colposcopist (Mayeaux & Cox, 2013; American Society for Colposcopy and Cervical Pathology [ASCCP] guidelines, Perkins et al, 2020). High-quality training and quality assurance programmes are essential for the competent practice of colposcopy.

Some attempts have been made to quantify qualitative descriptions into scoring systems, such as the Reid Colposcopic Index (RCI) (Reid & Scalzi, 1985) and the Swede score (Strander et al., 2005). It has been suggested that colposcopic

findings are best assessed formally using a scoring system (Prendiville & Sankaranarayanan, 2017; Ranga et al., 2017; Alan et al., 2020; Schulmeyer et al., 2020). However, some studies report better correlation of histology with colposcopic impression than with colposcopy-based quantitative scores. Li et al. (2017) compared the performance of the IFCPC colposcopic terminology, the RCI, and the Swede score for the identification of HSIL+ in 525 women in Shanghai, China, referred for colposcopy with suspicious-looking cervixes (including cervixes with abnormal bleeding or obvious contact bleeding, abnormal vaginal discharge, recurrent erosion, cervical polyp, leukoplakia, condyloma, gross neoplasm, irregular surface, or cervical canal stenosis, or barrel-like cervixes), abnormal cervical cytology (ASC-US+), or positive hrHPV test results. The results showed that the colposcopic accuracy was lower with the RCI and the Swede score than with the IFCPC classification; the sensitivity of the RCI for identification of HSIL+ was 38% and the specificity was 95%, and the sensitivity of the Swede score for identification of HSIL+ was 13% and the specificity was 99%; these scores are currently not widely used. For the IFCPC classification, the sensitivity for identification of HSIL+ was estimated to be 64% and the specificity 96%. However, no unique classification has yet been adopted in clinical practice worldwide.

(d)   Colposcopy training

Expertise in performing colposcopic examinations is attained and maintained by comprehensive training and experience with an adequate caseload. However, colposcopy training and assessment is neither uniform nor quality-assured worldwide. Even within the same country, there is considerable variation among colposcopists in training and experience (Wright, 2017).

Scientific colposcopy societies recognize the need to develop colposcopy standards for quality, and some have recently published training programmes (Public Health England, 2016; Mayeaux et al., 2017; Prendiville & Sankaranarayanan, 2017; AEPCC, 2018). Different societies propose different requirements, and few societies provide committees or infrastructures to support and oversee the training programmes (Moss et al., 2015). Nonetheless, most experts agree that training should involve supervised and unsupervised colposcopic assessment as well as attendance at clinical, histopathological, and cytopathological sessions (Public Health England, 2016; Prendiville, 2022).

Once a colposcopist is trained, performing a sufficient number of colposcopies per year is necessary to ensure continuing competence. The number differs between national colposcopy societies (Moss et al., 2013; Société Française de Colposcopie et de Pathologie Cervico-Vaginale, 2014; Public Health England, 2016; IFCPC, 2021), and some scientific groups do not specify the number of colposcopic evaluations needed per year to maintain competence (Mayeaux et al., 2017; Prendiville & Sankaranarayanan, 2017; AEPCC, 2018).

The systematic review by Mayeaux et al. (2017) of the different international guidelines for colposcopy quality described the wide variation between colposcopy societies in both colposcopy guidance and quality indicators, and emphasized the need for the standardization of guidance.

4.5.2 Accuracy of colposcopy in cytology-based screening

Despite the central role of colposcopy and colposcopy-directed biopsy in detecting cervical HSIL (Darragh et al., 2012), most of the available studies have evaluated colposcopy to assess the risk of underlying precancer or cancer. A limited number of studies have presented specific data for HSIL/CIN3+. However, recent studies evaluating colposcopy have shown that risk estimates for HSIL/CIN3+ were much less heterogeneous than results for HSIL/CIN2+; this probably reflects

the known variability and lack of reproducibility of CIN2/CIN3 diagnoses (Carreon et al., 2007; Herbert et al., 2008).

Four systematic reviews or meta-analyses have been performed on the accuracy of diagnostic colposcopy applied to women referred with abnormal cytology (Mitchell et al., 1998; Olaniyan, 2002; Mustafa et al., 2016; Brown & Tidy, 2019) (Table 4.36; web only; available from https://publications.iarc.fr/604). The most recent meta-analysis (Brown & Tidy, 2019), which included 10 973 women referred for colposcopy after abnormal cytology, reported a weighted mean sensitivity for histologically verified CIN2+ at a threshold of "any colposcopic abnormality" of 96% (range, 83–100%) and a weighted mean specificity of 34% (range, 5–67%). At a threshold of "high-grade colposcopic impression", the pooled sensitivity was 68% (range, 30–95%) and the pooled specificity was 76% (range, 48–97%). [The methods used for the calculation of diagnostic accuracy in clinical colposcopy trials are subject to several types of bias. The use of punch biopsies as the reference standard has been questioned in comparison with the results from excisional treatment after punch biopsy. It is important to consider that in many clinics biopsy is performed only when there is suspicion of disease. As a result, verification by biopsy is performed only when the outcome of colposcopy is positive and not when the outcome is negative. This form of bias results in overestimation of the sensitivity and underestimation of the specificity (Walter, 1999).]

Some analyses have attempted to eliminate this risk of bias. Underwood et al. (2012), in their systematic review, compared 7873 cases of colposcopy-directed cervical punch biopsy with their paired definitive histology from an excisional cervical biopsy or hysterectomy. At a threshold of "any colposcopic abnormality", the pooled sensitivity for a punch biopsy performed to diagnose a CIN2+ present in the surgical specimen was 91% (95% CI, 85–95%) and the pooled specificity was

25% (95% CI, 16–36%). At a threshold of "high-grade colposcopic impression", the pooled sensitivity was 80% (95% CI, 73–86%) and the pooled specificity was 63% (95% CI, 51–77%). Three subsequent retrospective studies (Kahramanoglu et al., 2019; Stuebs et al., 2019; Kim et al., 2020) evaluated the accuracy of colposcopy-directed biopsies with a paired specimen from an excisional treatment (including hysterectomy) and reported a sensitivity of punch biopsy for HSIL+/CIN2+ of 88–90% (92% in women with the entire TZ visible) and variable specificity of 37–59%. [None of these three studies specified whether the biopsies were performed for any colposcopy abnormality or only if a high-grade lesion was suspected.]

4.5.3 Colposcopy in HPV-based screening

When a transition is made from cytology-based strategies to strategies based on HPV testing, the central diagnostic role of colposcopy is maintained but the clinical characteristics of the patients and the number of women referred for colposcopy change profoundly. A major concern with switching from cytology to primary HPV screening is the management of HPV-positive women.

A study in 8369 women in the Guanacaste cohort study in Costa Rica (Porras et al., 2012) compared colposcopy characteristics and performance in women referred for colposcopy based on conventional cytology-based screening (ASC-US+) versus women with positive results in HPV-based screening (HPV typing using type-specific probes). The absolute risks of histological CIN2+ in women with abnormal colposcopy (or PPV) after cytology-based or HPV-based screening were similar (47.8% vs 41.5%, respectively; $P = 0.15$ for women aged 30 years or older). Similarly, there was no difference when ruling out histological CIN2+ in women with normal colposcopy (or NPV) in a cytology-based compared with an HPV-based

screening programme (87.2% vs 87.0%; $P = 0.92$ in women aged 30 years or older).

Colposcopy referrals for HPV-based screening compared with cytology-based screening were discussed in Section 4.4.2. To avoid overburdening the health-care system and overtreating women who are at low risk, a risk-based approach is needed to manage women with a positive HPV screening test result. A triage strategy enables the identification of HPV-positive women who are at higher risk of HSIL+ and who would most benefit from colposcopic examination. The different triage strategies were analysed in Section 4.4.7.

4.5.4 Random biopsies for diagnosis of CIN2+

In cervical cancer screening, it is especially important to rule out HSIL/CIN3+ in women with normal colposcopy, because most of these women do not undergo biopsy but are followed up.

In the Shanxi Province Cervical Cancer Screening Study I (SPOCCS I), Pretorius et al. (2004) evaluated colposcopies of 364 women in Shanxi Province, China, who were referred for colposcopy after an abnormal screening test with an entirely visible TZ in which all colposcopically abnormal areas were biopsied. If the colposcopic examination showed no lesion in a quadrant, a non-directed (random) biopsy was obtained within the TZ in that quadrant. In addition, endocervical curettage was performed after the cervical biopsies. The diagnosis of CIN2+ was made on a colposcopy-directed biopsy in 57% of women, a random biopsy in 37% of women, and an endocervical curettage in 6% of women.

Bekkers et al. (2008) evaluated the accuracy of colposcopy for the identification of HSIL in 6020 women in Melbourne, Australia, for whom the colposcopic impression was correlated with the histopathology result. In this study, colposcopy had a sensitivity of 60% and a PPV of 60% for the identification of HSIL, and the colposcopy-directed biopsies missed 39% of the HSIL. The

sensitivity of colposcopy for the identification of HSIL was significantly higher ($P < 0.001$) with junior colposcopists (66.7%) than with senior colposcopists (57.5%), but the PPV was significantly lower ($P < 0.001$) with junior colposcopists (56%) than with senior colposcopists (64%).

In the analysis of the two studies in Shanxi Province, China (SPOCCS I and II), which evaluated 1383 women with abnormal cytology who were referred for colposcopy (Pretorius et al., 2011), 25% of the 222 CIN3+ and 10% of the 31 cervical cancers were diagnosed in a random biopsy. [The sensitivity of colposcopy for diagnosis of CIN3+ varied significantly among the seven physicians performing colposcopy, from 29% to 93% ($P < 0.001$).]

Other studies did not report a benefit from random biopsies. In the Evaluating the Visual Appearance of Cervical Lesions in Relation to its Histological Diagnosis, Human Papillomavirus Genotype and Other Viral Parameters (EVAH) study in the Netherlands and Spain, van der Marel et al. (2014) evaluated the benefit of random biopsies performed in 610 women referred for colposcopy after an abnormal cytology result. Multiple directed biopsies were collected from lesions, and a non-directed biopsy of normal-appearing tissue was added if fewer than four biopsies were collected. In women with at least two lesion-directed biopsies, the yield for CIN2+ increased from 51.7% (95% CI, 45.7–57.7%) for one directed biopsy to 60.4% (95% CI, 54.4–66.2%; $P < 0.001$) for two biopsies. An additional 5% of CIN2+ were detected in biopsies from women who had been underdiagnosed by colposcopy.

In the Biopsy Study of the University of Oklahoma Health Sciences Center and the United States National Cancer Institute (Wentzensen et al., 2015), only 2% of all HSIL diagnosed in the 690 participants were detected by random biopsies performed on a normal-appearing TZ.

A retrospective follow-up study in the setting of the National Health Service (NHS) Cervical Screening Programme in England within the HPV or LBC pilot studies (Kelly et al., 2012) evaluated the risk of incident CIN2+ in 1063 HPV-positive women with low-grade cytological abnormalities (ASC-US or LSIL) who had a normal colposcopy with a completely visible TZ. In these women, the cumulative rate of CIN2+ at 3 years of follow-up was 4.4% (95% CI, 4–7%), independent of the age of the woman.

In the TOMBOLA trial, 884 women aged 20–59 years, with the same inclusion criteria as in the study of Kelly et al. (2012), were evaluated to determine the rate of CIN2+ over 3 years of cervical cytology follow-up including an exit colposcopic examination (Cruickshank et al., 2015). CIN2+ was detected in 5% of the women at the end of the study.

Munmany et al. (2018) evaluated the accuracy of colposcopic evaluation at the time of large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excision procedure (LEEP), to identify women with a previous biopsy diagnosis of HSIL/CIN2/3 with a low probability of dysplasia at the time of treatment. Of 162 women included in the study, 34 (21%) had a normal colposcopy with a completely visible TZ, and the absence of LSIL (CIN1) or HSIL/CIN2/3 in the excised specimen was confirmed in 28 (82%) of the 34 women.

Overall, these studies indicate that in countries in which colposcopy is part of a properly constructed, quality-assured programme, a normal colposcopy is associated with a very high NPV.

4.5.5 Risk-based colposcopy practice

Women referred for colposcopy after an abnormal screening result have a wide range of risk of harbouring a cervical lesion. Recently, it has been suggested that the risk of underlying histological HSIL can be estimated before colposcopic evaluation by assessing the information provided by the screening test (cytology and/or molecular test results). In this strategy, the practice of colposcopy and biopsy can be modified depending on the risk of precancer (Wentzensen et al., 2017; AEPCC, 2018; Perkins, et al., 2020). The risk of cervical precancer can be based on the results of the screening and follow-up tests (Dillner et al., 2008; Schiffman et al., 2015; Castle et al., 2016; Wentzensen et al., 2017; AEPCC, 2018; de Sanjosé et al., 2018; Egemen et al., 2020; Perkins, et al., 2020), as summarized in Table 4.37 (web only; available from https://publications.iarc.fr/604).

Moreover, information provided by the colposcopic impression may modify the need to perform multiple biopsies, including random biopsies (Wentzensen & Clarke, 2017; AEPCC, 2018; Silver et al., 2018; Egemen et al., 2020). A recent meta-analysis evaluated the risk strata based on combinations of cytology, HPV16 and/or HPV18 genotyping, and colposcopic impression (Silver et al., 2018). Eligible studies reported colposcopic impression and either cytology results or HPV16/18 partial genotyping results as well as a histological biopsy diagnosis from adult women. Women with < HSIL cytology who were HPV16/18-negative and had a normal colposcopic impression had the lowest risk of prevalent precancer and cancer (< 0.5% for HSIL/CIN3+). Women with at least two of the three high-risk results (i.e. HSIL cytology, HPV16- and/or HPV18-positive, and grade 2 changes at colposcopy) were at high risk (29–53% for HSIL/CIN3+), and women with all three of these high-risk results had the highest risk (> 70% for HSIL/CIN3+). Table 4.38 shows the levels (low, intermediate, and high) of risk of histological HSIL on the basis of cytology, HPV testing, and colposcopic findings.

On the basis of the current evidence, scientific societies have issued new colposcopy standards and risk-based management guidelines for the low-risk and high-risk groups of women based on

Table 4.38 Levels of risk of histological HSIL on the basis of cytology, HPV testing, and colposcopic findings

Low risk	Intermediate risk	High risk
Fulfil the following 3 criteria: • Cytology < HSIL • No HPV16/18 • Normal colposcopy	Cases not included in the other 2 risk groups	Fulfil at least 2 of the following 3 criteria: • Cytology ≥ HSIL, AGC, or ASC-H • HPV16 and/or HPV18 • Colposcopy showing grade 2 changes (high-grade/HSIL)

AGC, atypical glandular cells; ASC-H, atypical squamous cells, cannot exclude high-grade squamous epithelial lesions; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion.
Reproduced with permission from AEPCC (2018).

the available test results (cytology, HPV testing, and colposcopic impression) (Wentzensen et al., 2017; AEPCC, 2018; Perkins et al., 2020). Random biopsies should not be performed for women with < HSIL cytology who are HPV16/18-negative and have normal colposcopy. In contrast, in the case of abnormal colposcopy, even without any suspicion of cervical HSIL, cervical biopsy should be performed in women with HSIL cytology and/or HPV16- and/or HPV18-positive tests, particularly where adequate training and quality assurance are not in place. In women in the highest-risk group, the benefit of taking random biopsies from normal colposcopic areas within the TZ could also be considered. When multiple biopsies are taken and are negative, it is mandatory to provide close follow-up of the woman (i.e. every 6 months) (AEPCC, 2015), and if high-grade abnormalities (HSIL cytology and/or colposcopy showing grade 2 changes with negative biopsies) persist in the follow-up tests, type 3 excision (Bornstein et al., 2012) should be considered (Del Pino et al., 2010; AEPCC, 2015, 2018). In contrast, expedited excisional treatment (defined as excisional treatment without preceding colposcopy-directed biopsy demonstrating histological HSIL/CIN2+) is entirely appropriate in selected women at very high risk of harbouring HSIL/CIN3+, according to clinical guidelines (Wentzensen et al., 2017; Wright, 2017; Egemen et al., 2020; Perkins et al., 2020) (see also Section 1.2.5).

The main advantage of risk stratification is that the colposcopic examination and the biopsy strategy are adapted to the risk stratum. The colposcopist can either not perform a biopsy (in women at low risk) or perform expedited excisional treatment (in women at high risk). In women at intermediate risk, colposcopy-directed biopsies are appropriate. The potential benefit of biopsies in minimal acetowhite areas or when the colposcopy is normal (random biopsies) should be considered in each case (Waxman et al., 2017; Wentzensen et al., 2017; AEPCC, 2018).

4.5.6 Harmful effects of colposcopy

The harmful effects of colposcopy are (i) harms related to the procedure, (ii) harms linked with inadequate indication for colposcopy, and (iii) harms related to lack of experience or quality assurance.

(a) Harms related to the procedure

(i) Pain or discomfort

Although colposcopy is generally a well-tolerated examination, and therefore administration of analgesic drugs before the procedure is not recommended, some women may report discomfort due to the prolonged placing of the speculum or the application of acetic acid or iodine solution, or cramping or pain associated with the biopsy procedure (Khan et al., 2017;

AEPCC, 2018). In the TOMBOLA trial (Sharp et al., 2009), of the 401 women who underwent colposcopic examination (without biopsy or treatment), 18% (95% CI, 15–23%) reported some pain or physical discomfort when questioned at 6 weeks and 4 months after a colposcopy, and 5% (95% CI, 3–8%) reported that the discomfort was moderate to severe. O'Connor et al. (2017) reported that 59% of 248 women questioned at 4, 8, and 12 months after a colposcopy described pain (75% of the procedures included punch biopsies or conization). Pain during colposcopy is more closely related to the biopsy procedure or the treatment than to the colposcopy procedure itself. In addition, in the TOMBOLA trial (Sharp et al., 2009), of the women who underwent colposcopic examination (without biopsy or treatment), 18% (95% CI, 15–23%) reported pain; this proportion increased to 53% (95% CI, 44–61%) for those who underwent colposcopy and punch biopsy and to 67% (95% CI, 59–74%) for those who underwent colposcopy and excisional treatment (conization).

Pain and discomfort are generally experienced at the time of the procedure, but sometimes cramping can persist for a few hours. On the basis of two RCTs including 129 women, a Cochrane review concluded that there was no difference in pain relief between women undergoing colposcopy (without treatment) who received oral analgesics and those who received placebo or no treatment (mean difference, −3.51; 95% CI, −10.03 to 3.01 [low-quality evidence]) (Gajjar et al., 2016).

A prospective study conducted at Concord Women's Health Center in Israel including 101 women who underwent colposcopy reported a negative correlation between age and pain associated with the procedure (Pearson correlation coefficient, −0.220; $P < 0.05$) (Handelzalts et al., 2015).

(ii) Anxiety

Anxiety, worry, and fear are the feelings most commonly described during colposcopy (Galaal et al., 2011; O'Connor et al., 2016). In a systematic review evaluating psychological outcomes after colposcopy and related procedures, which included 16 studies (O'Connor et al., 2016), 60% of women undergoing colposcopy for the first time experienced anxiety (defined as an STAI score > 35), and 18% reported high anxiety levels (defined as an STAI score > 44); also, one third of the women undergoing colposcopy for the first time experienced distress or worry. The results of the procedure had impacts on the course of the negative feelings. At 6 weeks after the procedure, 21% of the women with a normal TZ and 42% of the women with an abnormal TZ still had significant distress. Moreover, in women with a normal TZ, distress and worry were significantly increased in those who reported pain or discharge after the procedure (Sharp et al., 2011, 2013).

Many women also report worry or anxiety in the period between the time of being notified of an abnormal screening result and the colposcopy appointment (Khan et al., 2017; Young et al., 2018). although it is unclear whether the diagnosis of an abnormal screening test or the colposcopy itself contributes to negative feelings (Khan et al., 2017). In general, women are less concerned about the procedure itself and are more anxious about having an HPV infection or cancer (see Section 4.4.8). Waller et al. (2007) evaluated the psychosocial impact of having a second positive HPV test result in 30 women undergoing cervical cancer screening who were HPV-positive with normal cytology at the first visit, and who attended for a repeat HPV test 12 months later. The study found that women appeared to be more distressed by a second positive HPV test result than by the first one. They also expressed a clear preference for immediate colposcopy over continued surveillance,

indicating that the anxiety was associated mainly with the screening result but also with a desire for a speedy resolution and fears about progression to cancer.

Colposcopy may also have a negative influence on sexual function. Seven studies included in the systematic review by O'Connor et al. (2016) assessed some aspect of sexual or psychosexual functioning after colposcopy. Although one study reported that the mean total score in the Female Sexual Function Index (FSFI) after colposcopy was above the threshold for female sexual disorder, the other studies comparing pre- with post-colposcopy sexual or psychosexual functioning reported conflicting results, with no consistent pattern of impact. [This secondary effect may be more closely related to abnormal screening test results than to the colposcopy procedure itself.]

Different approaches have been evaluated to reduce anxiety in women undergoing colposcopy after an abnormal screening test. Effective information and communication have consistently been shown to reduce anxiety (Kola et al., 2013; Handelzalts et al., 2015). Women who have not been extensively informed and are unaware of the possibility of experiencing side-effects score significantly higher for distress and anxiety during follow-up (O'Connor et al., 2017). Video colposcopy, which enables women to observe their own anatomy and watch what the colposcopist is doing, has been reported to reduce anxiety, in some studies (Kola et al., 2013) but not in others (Hilal et al., 2017).

Music therapy has been used to reduce anxiety associated with various medical procedures; however, in a recent meta-analysis, music therapy had no positive effect on reducing anxiety or pain or increasing satisfaction levels during colposcopy (Abdelhakim et al., 2019).

Most studies on the psychological impact of colposcopy have been performed in women undergoing colposcopy for the first time. However, compared with women undergoing subsequent colposcopic examinations, those undergoing colposcopy for the first time typically experience increased anxiety both before and after colposcopy and display a tendency to seek information about the procedure (Handelzalts et al., 2015).

(iii)   Anaphylactic reaction to iodine solution

Isolated examples of allergic reactions to iodine solution have been described. These include pruritus, vaginal oedema, hypotension, tachycardia, and breathing difficulties. The symptoms usually disappear upon withdrawal of the iodine solution (Indraccolo et al., 2009).

(b)   Harms linked with inadequate indication for colposcopy

Although colposcopy was initially used as a tool for primary screening of cervical cancer and precancer, an increased understanding of the natural history of HPV infection and its progression to cervical neoplasia has recently reduced the indications for colposcopy. Strict adherence to indications for colposcopy (Table 4.33) minimizes the side-effects associated with inappropriate use of this procedure.

(c)   Harms related to lack of experience or quality assurance

Colposcopy requires adequate training and experience to attain proficiency, assure quality, and maintain competence in performing the procedure. The proportion of false-negative results of colposcopy (women with HSIL/CIN2+ classified as being disease-free) correlates directly with the expertise of the colposcopist.

As mentioned above, one study showed significantly higher sensitivity for the identification of HSIL when performed by junior colposcopists (with 0–2 years of experience in colposcopy) compared with senior colposcopists (with > 3 years of experience) (66.7% vs 57.5%; $P < 0.001$), but a significantly lower PPV (56% vs 64%; $P < 0.001$) (Bekkers et al., 2008).

A retrospective analysis comparing the precision of diagnosis by colposcopy-directed biopsy with the final histological outcome of the surgical specimen in 641 women showed a risk of underdiagnosis of HSIL (false negativity) of 12% when the colposcopist had 0–5 years of experience and of 8% when the colposcopist had more than 10 years of experience (Stuebs et al., 2019).

References

Abdelhakim AM, Samy A, Abbas AM (2019). Effect of music in reducing patient anxiety during colposcopy: a systematic review and meta-analysis of randomized controlled trials. *J Gynecol Obstet Hum Reprod.* 48(10):855–61. doi:10.1016/j.jogoh.2019.07.007 PMID:31276848

AEPCC (2015). Guía: prevención del cáncer de cuello de útero. Asociación Española de Patología Cervical y Colposcopia. [in Spanish] Available from: http://www.aepcc.org/wp-content/uploads/2016/01/AEPCC_revista02.pdf.

AEPCC (2018). Guía de colposcopia. Estándares de calidad. Asociación Española de Patología Cervical y Colposcopia. [in Spanish] Available from: http://www.aepcc.org/wp-content/uploads/2019/01/AEPCC_revista10-colposcopia-web.pdf.

Alan M, Gunyeli I, Gultekin M, Sancı M, Yuce K (2020). Correlation of Swede score colposcopy scoring system and histopathological results in patients with high-risk HPV infection other than HPV16 and 18. *Int J Gynecol Cancer.* 30(1):35–40. doi:10.1136/ijgc-2019-000932 PMID:31792083

Bappa LA, Yakasai IA (2013). Colposcopy: the scientific basis. *Ann Afr Med.* 12(2):86–9. doi:10.4103/1596-3519.112396 PMID:23713014

Bekkers RL, van de Nieuwenhof HP, Neesham DE, Hendriks JH, Tan J, Quinn MA (2008). Does experience in colposcopy improve identification of high grade abnormalities? *Eur J Obstet Gynecol Reprod Biol.* 141(1):75–8. doi:10.1016/j.ejogrb.2008.07.007 PMID:18760872

Beller FK, Khatamee M (1966). Evaluation of punch biopsy of the cervix under direct colposcopic observation (target punch biopsy). *Obstet Gynecol.* 28(5):622–5. PMID:5923541

Beyer DA, Rody A, Cirkel C, Schmidt N, Neumann K (2017). Mandatory colposcopic findings of severe cervical dysplasia. Are there key-signs that need our special attention? *J Gynecol Obstet Hum Reprod.* 46(8):643–6. doi:10.1016/j.jogoh.2017.07.002 PMID:28698072

Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, et al. (2012). 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. *Obstet Gynecol.* 120(1):166–72. doi:10.1097/AOG.0b013e318254f90c PMID:22914406

Brown BH, Tidy JA (2019). The diagnostic accuracy of colposcopy – a review of research methodology and impact on the outcomes of quality assurance. *Eur J Obstet Gynecol Reprod Biol.* 240:182–6. doi:10.1016/j.ejogrb.2019.07.003 PMID:31302386

Carreon JD, Sherman ME, Guillén D, Solomon D, Herrero R, Jerónimo J, et al. (2007). CIN2 is a much less reproducible and less valid diagnosis than CIN3: results from a histological review of population-based cervical samples. *Int J Gynecol Pathol.* 26(4):441–6. doi:10.1097/pgp.0b013e31805152ab PMID:17885496

Castle PE, Aslam S, Behrens C (2016). Cervical precancer and cancer risk by human papillomavirus status and cytologic interpretation: implications for risk-based management. *Cancer Epidemiol Biomarkers Prev.* 25(12):1595–9. doi:10.1158/1055-9965.EPI-16-0330 PMID:27587789

Colgan TJ, Lickrish GM (1990). The topography and invasive potential of cervical adenocarcinoma *in situ*, with and without associated squamous dysplasia. *Gynecol Oncol.* 36(2):246–9. doi:10.1016/0090-8258(90)90182-K PMID:2298414

Cruickshank ME, Cotton SC, Sharp L, Smart L, Walker LG, Little J; TOMBOLA Group (2015). Management of women with low grade cytology: how reassuring is a normal colposcopy examination? *BJOG.* 122(3):380–6. doi:10.1111/1471-0528.12932 PMID:24947656

Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, et al.; Members of LAST Project Work Groups (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. [Erratum in: Arch Pathol Lab Med. 2013 137(6):738] *Arch Pathol Lab Med.* 136(10):1266–97. doi:10.5858/arpa.LGT200570 PMID:22742517

de Sanjosé S, Rodríguez-Salés V, Bosch XF, Ibañez R, Bruni L (2018). Population-based e-records to evaluate HPV triage of screen-detected atypical squamous cervical lesions in Catalonia, Spain, 2010–15. *PLoS One.* 13(11):e0207812. doi:10.1371/journal.pone.0207812 PMID:30475876

Del Pino M, Torne A, Alonso I, Mula R, Masoller N, Fuste V, et al. (2010). Colposcopy prediction of progression in human papillomavirus infections with minor cervical lesions. *Obstet Gynecol.* 116(6):1324–31. doi:10.1097/AOG.0b013e3181f74885 PMID:21099598

Dillner J, Rebolj M, Birembaut P, Petry KU, Szarewski A, Munk C, et al. (2008). Long term predictive values of cytology and human papillomavirus testing in cervical

cancer screening: joint European cohort study. *BMJ*. 337:a1754. doi:10.1136/bmj.a1754 PMID:18852164

Egemen D, Cheung LC, Chen X, Demarco M, Perkins RB, Kinney W, et al. (2020). Risk estimates supporting the 2019 ASCCP Risk-based Management Consensus Guidelines. *J Low Genit Tract Dis*. 24(2):132–43. doi:10.1097/LGT.0000000000000529 PMID:32243308

Ferris DG, Litaker M; ALTS Group (2005). Interobserver agreement for colposcopy quality control using digitized colposcopic images during the ALTS trial. *J Low Genit Tract Dis*. 9(1):29–35. doi:10.1097/00128360-200501000-00007 PMID:15870519

Gajjar K, Martin-Hirsch PPL, Bryant A, Owens GL (2016). Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment. *Cochrane Database Syst Rev*. 7(7):CD006120. doi:10.1002/14651858.CD006120.pub4 PMID:27428114

Galaal K, Bryant A, Deane KHO, Al-Khaduri M, Lopes AD (2011). Interventions for reducing anxiety in women undergoing colposcopy. *Cochrane Database Syst Rev*. (12):CD006013. doi:10.1002/14651858.CD006013.pub3 PMID:22161395

Handelzalts JE, Krissi H, Levy S, Broitman M, Binyamin L, Peled Y (2015). Multidimensional associations of pain and anxiety before and after colposcopy. *Int J Gynaecol Obstet*. 131(3):297–300. doi:10.1016/j.ijgo.2015.05.038 PMID:26386494

Herbert A, Arbyn M, Bergeron C (2008). Why CIN3 and CIN2 should be distinguished on histological reports. *Cytopathology*. 19(1):63–4. doi:10.1111/j.1365-2303.2006.00539.x PMID:18205632

Hilal Z, Alici F, Tempfer CB, Seebacher V, Rezniczek GA (2017). Video colposcopy for reducing patient anxiety during colposcopy: a randomized controlled trial. *Obstet Gynecol*. 130(2):411–9. doi:10.1097/AOG.0000000000002127 PMID:28697117

Hilgarth M, Menton M (1996). The colposcopic screening. *Eur J Obstet Gynecol Reprod Biol*. 65(1):65–9. doi:10.1016/0028-2243(95)02306-D PMID:8706960

Hinselmann H (1925). Verbesserung der Inspektionsmöglichkeiten von Vulva, Vagina und Portio. *Munch Med Wochenschr*. 72:1733.

IFCPC (2021). IFCPC-IARC training course in colposcopy and the prevention of cervical cancer. Rockwell (MD), USA: International Federation of Cervical Pathology and Colposcopy. Available from: https://ifcpc.org/education.

Indraccolo U, Palombino K, Greco P (2009). Anaphylactic-like reaction to Lugol solution during colposcopy. *South Med J*. 102(1):96–7. doi:10.1097/SMJ.0b013e31818894f4 PMID:19077773

Jordan JA (1985). Colposcopy in the diagnosis of cervical cancer and precancer. *Clin Obstet Gynaecol*. 12(1):67–76. PMID:3995857

Kahramanoglu I, Demirkiran F, Turan H, Bese T, Yilmaz N, Ilvan S, et al. (2019). The use of colposcopic punch biopsy in the management of abnormal cervical cytology: a 5-year retrospective audit. *J Obstet Gynaecol*. 39(1):110–4. doi:10.1080/01443615.2018.1468740 PMID:30230394

Kelly RS, Walker P, Kitchener H, Moss SM (2012). Incidence of cervical intraepithelial neoplasia grade 2 or worse in colposcopy-negative/human papillomavirus-positive women with low-grade cytological abnormalities. *BJOG*. 119(1):20–5. doi:10.1111/j.1471-0528.2011.02970.x PMID:21624034

Khan MJ, Werner CL, Darragh TM, Guido RS, Mathews C, Moscicki AB, et al. (2017). ASCCP Colposcopy Standards: role of colposcopy, benefits, potential harms, and terminology for colposcopic practice. *J Low Genit Tract Dis*. 21(4):223–9. doi:10.1097/LGT.0000000000000338 PMID:28953110

Kim SI, Kim SJ, Suh DH, Kim K, No JH, Kim YB (2020). Pathologic discrepancies between colposcopy-directed biopsy and loop electrosurgical excision procedure of the uterine cervix in women with cytologic high-grade squamous intraepithelial lesions. *J Gynecol Oncol*. 31(2):e13. doi:10.3802/jgo.2020.31.e13 PMID:31912671

Kola S, Walsh JC, Hughes BM, Howard S (2013). Matching intra-procedural information with coping style reduces psychophysiological arousal in women undergoing colposcopy. *J Behav Med*. 36(4):401–12. doi:10.1007/s10865-012-9435-z PMID:22729966

Leeson SC, Alibegashvili T, Arbyn M, Bergeron C, Carriero C, Mergui JL, et al. (2014). The future role for colposcopy in Europe. *J Low Genit Tract Dis*. 18(1):70–8. doi:10.1097/LGT.0b013e318286b899 PMID:23774077

Li Y, Duan X, Sui L, Xu F, Xu S, Zhang H, et al. (2017). Closer to a uniform language in colposcopy: study on the potential application of 2011 International Federation for Cervical Pathology and Colposcopy terminology in clinical practice. *Biomed Res Int*. 2017:8984516. doi:10.1155/2017/8984516 PMID:28626767

Mayeaux EJ, Cox JT, editors (2013). Colposcopia: texto y atlas. 3rd ed. Barcelona, Spain: Lippincott Williams & Wilkins.

Mayeaux EJ Jr, Novetsky AP, Chelmow D, Choma K, Garcia F, Liu AH, et al. (2017). Systematic review of international colposcopy quality improvement guidelines. *J Low Genit Tract Dis*. 21(4):249–57. doi:10.1097/LGT.0000000000000344 PMID:28953114

Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R (1998). Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol*. 91(4):626–31. doi:10.1097/00006250-199804000-00029 PMID:9540955

Moss EL, Arbyn M, Dollery E, Leeson S, Petry KU, Nieminen P, et al. (2013). European Federation of Colposcopy quality standards Delphi consultation. *Eur J Obstet Gynecol Reprod Biol.* 170(1):255–8. doi:10.1016/j.ejogrb.2013.06.032 PMID:23891389

Moss EL, Redman CWE, Arbyn M, Dollery E, Petry KU, Nieminen P, et al. (2015). Colposcopy training and assessment across the member countries of the European Federation for Colposcopy. *Eur J Obstet Gynecol Reprod Biol.* 188:124–8. doi:10.1016/j.ejogrb.2015.03.012 PMID:25839437

Munmany M, Torné A, Nonell R, Barnadas E, Luqui N, Ordi J, et al. (2018). Colposcopy evaluation at the time of loop electrosurgical excision procedure may avoid unnecessary treatment. *J Low Genit Tract Dis.* 22(4):367–74. doi:10.1097/LGT.0000000000000410 PMID:29957657

Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. (2016). Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. *Int J Gynaecol Obstet.* 132(3):259–65. doi:10.1016/j.ijgo.2015.07.024 PMID:26851054

O'Connor M, Gallagher P, Waller J, Martin CM, O'Leary JJ, Sharp L; Irish Cervical Screening Research Consortium (CERVIVA) (2016). Adverse psychological outcomes following colposcopy and related procedures: a systematic review. *BJOG.* 123(1):24–38. doi:10.1111/1471-0528.13462 PMID:26099164

O'Connor M, O'Brien K, Waller J, Gallagher P, D'Arcy T, Flannelly G, et al.; Irish Cervical Screening Research Consortium (CERVIVA) (2017). Physical after-effects of colposcopy and related procedures, and their inter-relationship with psychological distress: a longitudinal survey. *BJOG.* 124(9):1402–10.doi:10.1111/1471-0528.14671 PMID:28374937

Olaniyan OB (2002). Validity of colposcopy in the diagnosis of early cervical neoplasia – a review. *Afr J Reprod Health.* 6(3):59–69. doi:10.2307/3583258 PMID:12685410

Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al.; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee (2020). 2019 ASCCP Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors. [Erratum in: J Low Genit Tract Dis. 2020 24(4):427] *J Low Genit Tract Dis.* 24(2):102–31. doi:10.1097/LGT.0000000000000525 PMID:32243307

Porras C, Wentzensen N, Rodríguez AC, Morales J, Burk RD, Alfaro M, et al. (2012). Switch from cytology-based to human papillomavirus test-based cervical screening: implications for colposcopy. *Int J Cancer.* 130(8):1879–87. doi:10.1002/ijc.26194 PMID:21607948

Prendiville W (2022). A systematic approach to colposcopic examination. In: Prendiville W, del Pino M, Wentzensen N, editors. Core topics in cervical dysplasia and colposcopy. Cambridge, UK: Cambridge University Press. (forthcoming)

Prendiville W, Sankaranarayanan R (2017). Colposcopy and treatment of cervical precancer (IARC Technical Publications, No. 45). Lyon, France: International Agency for Research on Cancer. Available from: https://publications.iarc.fr/555.

Pretorius RG, Belinson JL, Burchette RJ, Hu S, Zhang X, Qiao YL (2011). Regardless of skill, performing more biopsies increases the sensitivity of colposcopy. *J Low Genit Tract Dis.* 15(3):180–8. doi:10.1097/LGT.0b013e3181fb4547 PMID:21436729

Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. (2004). Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. *Am J Obstet Gynecol.* 191(2):430–4. doi:10.1016/j.ajog.2004.02.065 PMID:15343217

Public Health England (2016). NHS Cervical Screening Programme: colposcopy and programme management. 3rd ed. London, UK: Public Health England. Available from: https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management.

Ranga R, Rai S, Kumari A, Mathur S, Kriplani A, Mahey R, et al. (2017). A comparison of the strength of association of Reid Colposcopic Index and Swede score with cervical histology. *J Low Genit Tract Dis.* 21(1):55–8. doi:10.1097/LGT.0000000000000278 PMID:27851696

Reid R, Campion MJ (1989). Lesiones del cuello uterino relacionadas con papilomavirus humano: biología y características colposcópica. [in Spanish] *Clin Ostet Ginecol.* 1:151–73.

Reid R, Scalzi P (1985). Genital warts and cervical cancer. VII. An improved colposcopic index for differentiating benign papillomaviral infections from high-grade cervical intraepithelial neoplasia. *Am J Obstet Gynecol.* 153(6):611–8. doi:10.1016/S0002-9378(85)80244-1 PMID:2998190

Ruiz Moreno JA (2010). Pasado, presente y futuro de la colposcopia: perspectiva de un profesional en tracto genital inferior. [in Spanish] *Arch Méd Actual Trac Gen Inf.* 2(2):27–34. Available from: http://www.medigraphic.com/pdfs/archivostgi/tgi-2010/tgi102e.pdf.

Schiffman M, Vaughan LM, Raine-Bennett TR, Castle PE, Katki HA, Gage JC, et al. (2015). A study of HPV typing for the management of HPV-positive ASC-US cervical cytologic results. *Gynecol Oncol.* 138(3):573–8. doi:10.1016/j.ygyno.2015.06.040 PMID:26148763

Schiller W (1933). Early diagnosis of carcinoma of the cervix. *Surg Gynecol Obstet.* 56:210–22.

Schulmeyer CE, Stübs F, Gass P, Renner SK, Hartmann A, Strehl J, et al. (2020). Correlation between referral cytology and in-house colposcopy-guided cytology for detecting early cervical neoplasia. *Arch Gynecol*

Obstet. 301(1):263–71. doi:10.1007/s00404-019-05389-1 PMID:31811416

Sharp L, Cotton S, Carsin AE, Gray N, Thornton A, Cruickshank M, et al.; TOMBOLA Group (2013). Factors associated with psychological distress following colposcopy among women with low-grade abnormal cervical cytology: a prospective study within the Trial Of Management of Borderline and Other Low-grade Abnormal smears (TOMBOLA). *Psychooncology*. 22(2):368–80. doi:10.1002/pon.2097 PMID:22162138

Sharp L, Cotton S, Cochran C, Gray N, Little J, Neal K, et al.; TOMBOLA Group (2009). After-effects reported by women following colposcopy, cervical biopsies and LLETZ: results from the TOMBOLA trial. *BJOG*. 116(11):1506–14. doi:10.1111/j.1471-0528.2009.02263.x PMID:19583712

Sharp L, Cotton S, Gray N, Avis M, Russell I, Walker L, et al.; TOMBOLA Group (2011). Long-term psychosocial impact of alternative management policies in women with low-grade abnormal cervical cytology referred for colposcopy: a randomised controlled trial. *Br J Cancer*. 104(2):255–64. doi:10.1038/sj.bjc.6606042 PMID:21179033

Silver MI, Andrews J, Cooper CK, Gage JC, Gold MA, Khan MJ, et al. (2018). Risk of cervical intraepithelial neoplasia 2 or worse by cytology, human papillomavirus 16/18, and colposcopy impression: a systematic review and meta-analysis. *Obstet Gynecol*. 132(3):725–35. doi:10.1097/AOG.0000000000002812 PMID:30095780

Société Française de Colposcopie et de Pathologie Cervico-Vaginale (2014). Charte de qualité en colposcopie. Available from: http://www.societe-colposcopie.com/grand-public/charte-de-qualite-en-colposcopie.

Soutter WP (1993). A practical guide to colposcopy. New York (NY), USA: Oxford University Press.

Stafl A (1976). New nomenclature for colposcopy. Report of the committee on terminology. *Obstet Gynecol*. 48(1):123–4. PMID:945521

Stafl A, Wilbanks GD (1991). An international terminology of colposcopy: report of the Nomenclature Committee of the International Federation of Cervical Pathology and Colposcopy. *Obstet Gynecol*. 77(2):313–4. doi:10.1097/00006250-199102000-00032 PMID:1988900

Strander B, Ellström-Andersson A, Franzén S, Milsom I, Rådberg T (2005). The performance of a new scoring system for colposcopy in detecting high-grade dysplasia in the uterine cervix. *Acta Obstet Gynecol Scand*. 84(10):1013–7. doi:10.1111/j.0001-6349.2005.00895.x PMID:16167921

Stuebs FA, Schulmeyer CE, Mehlhorn G, Gass P, Kehl S, Renner SK, et al. (2019). Accuracy of colposcopy-directed biopsy in detecting early cervical neoplasia: a

retrospective study. *Arch Gynecol Obstet*. 299(2):525–32. doi:10.1007/s00404-018-4953-8 PMID:30367250

Underwood M, Arbyn M, Parry-Smith W, De Bellis-Ayres S, Todd R, Redman CW, et al. (2012). Accuracy of colposcopy-directed punch biopsies: a systematic review and meta-analysis. *BJOG*. 119(11):1293–301. doi:10.1111/j.1471-0528.2012.03444.x PMID:22882742

van der Marel J, van Baars R, Rodriguez A, Quint WGV, van de Sandt MM, Berkhof J, et al. (2014). The increased detection of cervical intraepithelial neoplasia when using a second biopsy at colposcopy. *Gynecol Oncol*. 135(2):201–7. doi:10.1016/j.ygyno.2014.08.040 PMID:25204846

van Niekerk WA, Dunton CJ, Richart RM, Hilgarth M, Kato H, Kaufman RH, et al. (1998). Colposcopy, cervicography, speculoscopy and endoscopy: IAC Task Force summary. *Acta Cytol*. 42(1):33–49. doi:10.1159/000331533 PMID:9479322

Vercellino GF, Erdemoglu E, Chiantera V, Vasiljeva K, Drechsler I, Cichon G, et al. (2013). Validity of the colposcopic criteria inner border sign, ridge sign, and rag sign for detection of high-grade cervical intraepithelial neoplasia. *Obstet Gynecol*. 121(3):624–31. doi:10.1097/AOG.0b013e3182835831 PMID:23635627

Walker P, Dexeus S, De Palo G, Barrasso R, Campion M, Girardi F, et al.; Nomenclature Committee of the International Federation for Cervical Pathology and Colposcopy (2003). International terminology of colposcopy: an updated report from the International Federation for Cervical Pathology and Colposcopy. *Obstet Gynecol*. 101(1):175–7. doi:10.1016/S0029-7844(02)02581-4 PMID:12517664

Waller J, McCaffery K, Kitchener H, Nazroo J, Wardle J (2007). Women's experiences of repeated HPV testing in the context of cervical cancer screening: a qualitative study. *Psychooncology*. 16(3):196–204. doi:10.1002/pon.1053 PMID:16858719

Walter SD (1999). Estimation of test sensitivity and specificity when disease confirmation is limited to positive results. *Epidemiology*. 10(1):67–72. doi:10.1097/00001648-199901000-00012 PMID:9888282

Waxman AG, Conageski C, Silver MI, Tedeschi C, Stier EA, Apgar B, et al. (2017). ASCCP Colposcopy Standards: how do we perform colposcopy? Implications for establishing standards. *J Low Genit Tract Dis*. 21(4):235–41. doi:10.1097/LGT.0000000000000336 PMID:28953112

Wentzensen N, Clarke MA (2017). From clinical epidemiology to practice recommendations: knowledge gaps and uncertainty in the management of anal precancers. *Cancer*. 123(23):4530–4. doi:10.1002/cncr.31033 PMID:28949415

Wentzensen N, Schiffman M, Silver MI, Khan MJ, Perkins RB, Smith KM, et al. (2017). ASCCP Colposcopy Standards: risk-based colposcopy practice. *J Low Genit Tract Dis*. 21(4):230–4. doi:10.1097/LGT.0000000000000334 PMID:28953111

Wentzensen N, Walker JL, Gold MA, Smith KM, Zuna RE, Mathews C, et al. (2015). Multiple biopsies and detection of cervical cancer precursors at colposcopy. *J Clin Oncol.* 33(1):83–9. doi:10.1200/JCO.2014.55.9948 PMID:25422481

Wright TC Jr (2017). The new ASCCP Colposcopy Standards. *J Low Genit Tract Dis.* 21(4):215. doi:10.1097/LGT.0000000000000337 PMID:28953108

Young A, Cotton S, Cruickshank ME (2018). Information needs of young women vaccinated against HPV attending colposcopy: a qualitative study. *BMC Womens Health.* 18(1):200. doi:10.1186/s12905-018-0691-0 PMID:30541542

4.6 Emerging technologies

Recent advances in understanding of HPV-associated carcinogenesis have led to the development and evaluation of many new technologies and approaches for cervical cancer screening, triage, management, and diagnosis. Three types of approaches for the detection of cervical precancer are distinguished: those based on visual, cytological, and molecular technologies.

Several systematic approaches to assess the potential use of a biomarker in cervical cancer screening and management have been proposed (Arbyn et al., 2009; Wentzensen & Wacholder, 2013). Established guidelines for diagnostic research (the Standards for Reporting of Diagnostic Accuracy Studies [STARD] statement) have been adapted for technology development for cervical cancer screening (Arbyn et al., 2009). Five phases of technology evaluation are formally distinguished: (1) preclinical exploratory studies, (2) clinical validation studies, (3) retrospective biobank studies in the target population, (4) prospective screening studies, and (5) prospective intervention studies. Although this framework provides important guidance for technology development, not all of these steps are required for all technologies, and the sequence may vary depending on the clinical indication and the availability of suitable research studies. The evaluation of a technology must occur in the context of its potential use, because diagnostic accuracy requirements differ depending on whether the technology is used in screening, triage, or disease confirmation. Here, the term "emerging technology" is used when the discovery processes have been completed and the early steps of technology evaluation are under way (i.e. phases 1–3).

The process from discovery and development to clinical implementation is complex and involves many stakeholders, including researchers, industry, regulatory authorities, and professional societies that develop guidelines (Wentzensen & Silver, 2016). It can take a long time from initial discovery to clinical implementation. For example, HPV DNA testing was initially developed in the 1980s but did not enter clinical practice until 20 years later. The timeline from discovery to clinical practice is now shorter, because of the better understanding of the natural history of cervical cancer and the much accelerated technology development.

Because most discovered biomarkers do not make it into clinical practice, it is important to identify likely failures early in the evaluation process, enabling researchers to focus on the most promising leads (Wentzensen & Wacholder, 2013). The most important criterion for a biomarker is whether the test result will improve clinical management; if not, the test may be useless. Successful biomarker development usually relies on a commercial party to invest in assay development and regulatory approval. Therefore, barriers to bringing a promising biomarker into clinical practice may be the lack of intellectual property, or relatively limited clinical indication, which may result in too small a commercial market.

Of the molecular technologies summarized here, some were developed several years ago but have not been sufficiently validated for consideration of clinical use or have not been translated from the research setting to a commercially available test, for various reasons. Other novel technologies are rapidly progressing through the evaluation process, such as AI-based visual and cytological methods, as well as host and viral DNA methylation markers, which can be expected to appear in extensive clinical validation studies very soon.

Fig. 4.8 Pathway to the development of new technologies
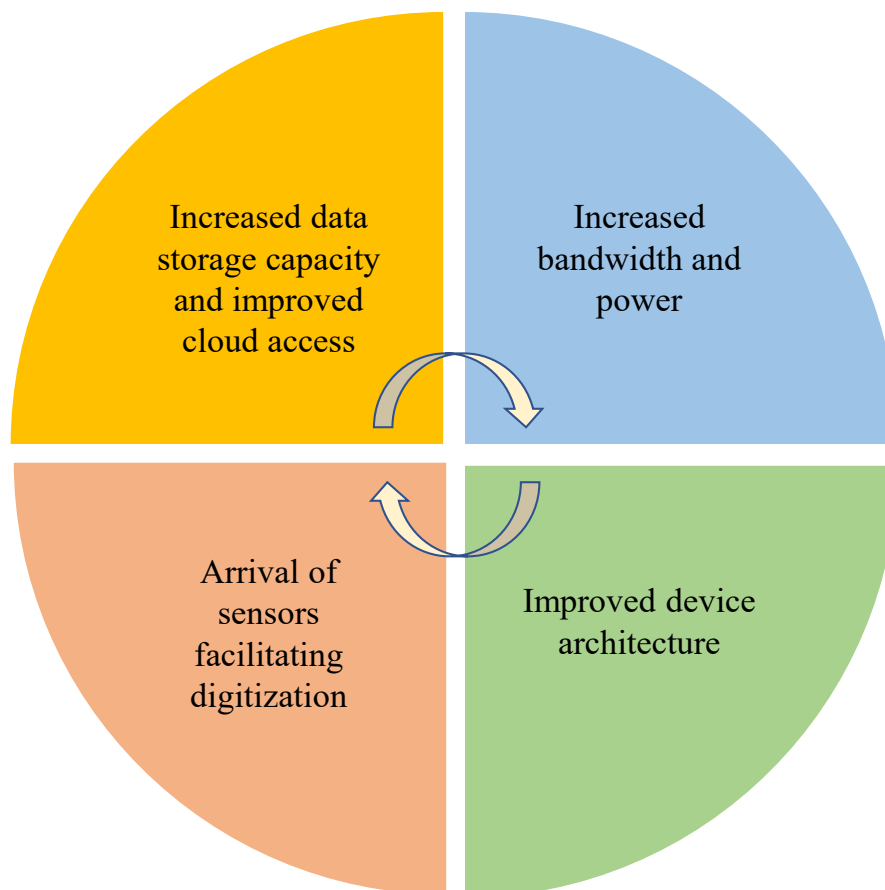
Created by the Working Group.

4.6.1 Emerging technologies using artificial intelligence

AI is having an impact on many scientific disciplines, including medicine. As the power of computer software has increased, the size of the hardware has decreased, and as Internet bandwidth and electronic storage capacity have improved, it has become possible to deliver accurate image-recognition systems in very small, cloud-independent devices that incorporate comprehensive systems for management of clinical data and images ([Fig. 4.8](#)). Convolutional neural networks (CNNs) are commonly used for the analysis and classification of visual images;

they are increasingly being used in medical diagnostics, such as in the classification of benign or malignant lung tumours ([Hussein et al., 2017](#)), in skin cancer ([Esteva et al., 2017](#)), in retinopathy ([Ting et al., 2017](#)), in the classification of colorectal polyps ([Wei et al., 2020](#)), in breast cancer ([McKinney et al., 2020](#)), and in the detection of cardiological abnormalities ([Islam et al., 2017](#)). Recently, these approaches have also been applied to automated and biomarker-enhanced cervical cytology ([Schiffman et al., 2017](#); [Wentzensen et al., 2021](#)).

(a) AI-based automated visual evaluation

Even with adequate training and quality assurance measures in place, visual inspection of the cervix is a highly subjective procedure, including determining the adequacy of the examination, the type of the TZ, and the diagnostic impression. Furthermore, comprehensive training to the level of independent practice can take 6–18 months. A major but not exclusive part of this training is in image recognition, which to date has been learned largely within a live clinical setting. The concept of training a computer to recognize abnormality by "learning" the relevant features from a large image bank of known histopathology has obvious appeal. If that computational power can be harnessed in small, inexpensive, and user-friendly image-capture systems, the inadequacies of current visual examination methods could be addressed without the need for expensive training or adjunctive systems. As a laboratory-independent and reusable device, this technology could replace or complement current visual-based screening and triage approaches in LMICs. It may also negate the need for individual colposcopy expertise in screen-positive women who are not suitable for ablative treatment as part of a screen-and-treat protocol. AI can be used innovatively to train service providers and for quality control. Currently, no system has been properly evaluated in a live or real-world setting.

(i) Technical description

Training a model to discriminate between one image and another is now feasible, thanks to improved technology. Also, computing power has increased exponentially, and large, appropriately labelled image banks are available. Currently, for the detection of squamous cervical precancer, the clinically important discriminatory threshold is between normal or LSIL and HSIL. Therefore, algorithms in cervical precancer detection have focused on this dichotomous division. Training a CNN to discriminate between two distinct epithelial appearances within the squamous epithelium of the TZ involves exposing the model to a large series of adequate cervical images of known severity (i.e. supported by histopathology). Moreover, specific features on the cervical image may also be labelled by experts for a model to process. The CNN may then categorize cervical images into one of the two categories (≤ LSIL or HSIL) by outputting the probability that a given image belongs to either category.

During training, the CNN receives as inputs images from the training data set and adjusts its parameters to minimize the error between its predictions and the ground truth (i.e. colposcopically or histologically verified disease status) of the training set. Thus, the CNN is fitted to the training data set, learning the relevant features from the training data set, which enables it to increase the number of correct predictions. This process is illustrated in Fig. 4.9 (Hu et al., 2019). While the model is being trained on the training data set, the discriminative performance of the model is evaluated in a validation set. The purpose of the validation set is to evaluate the performance of the model on data that it has not been fitted to during the training process. Models with different selected hyperparameters can be trained in this way until a model that performs optimally on the validation set is determined. This yields a final trained model that can then be evaluated on a test set of images to assess its generalizability to predict cervical disease.

In general, the larger the training set, the higher the accuracy of the model. A viable model is often only as good as the quality of the images on which it is trained and the labels, or the robustness of the disease end-points, associated with these images. In many medical applications, there is often an imbalance between the number of images in each category; for example, in most cervical precancer image banks there are more images of ≤ LSIL than of HSIL. This imbalance can affect the training and validation process for the development of the model. The

Fig. 4.9 System architecture of the automated visual evaluation algorithm used by Hu et al. (2019)
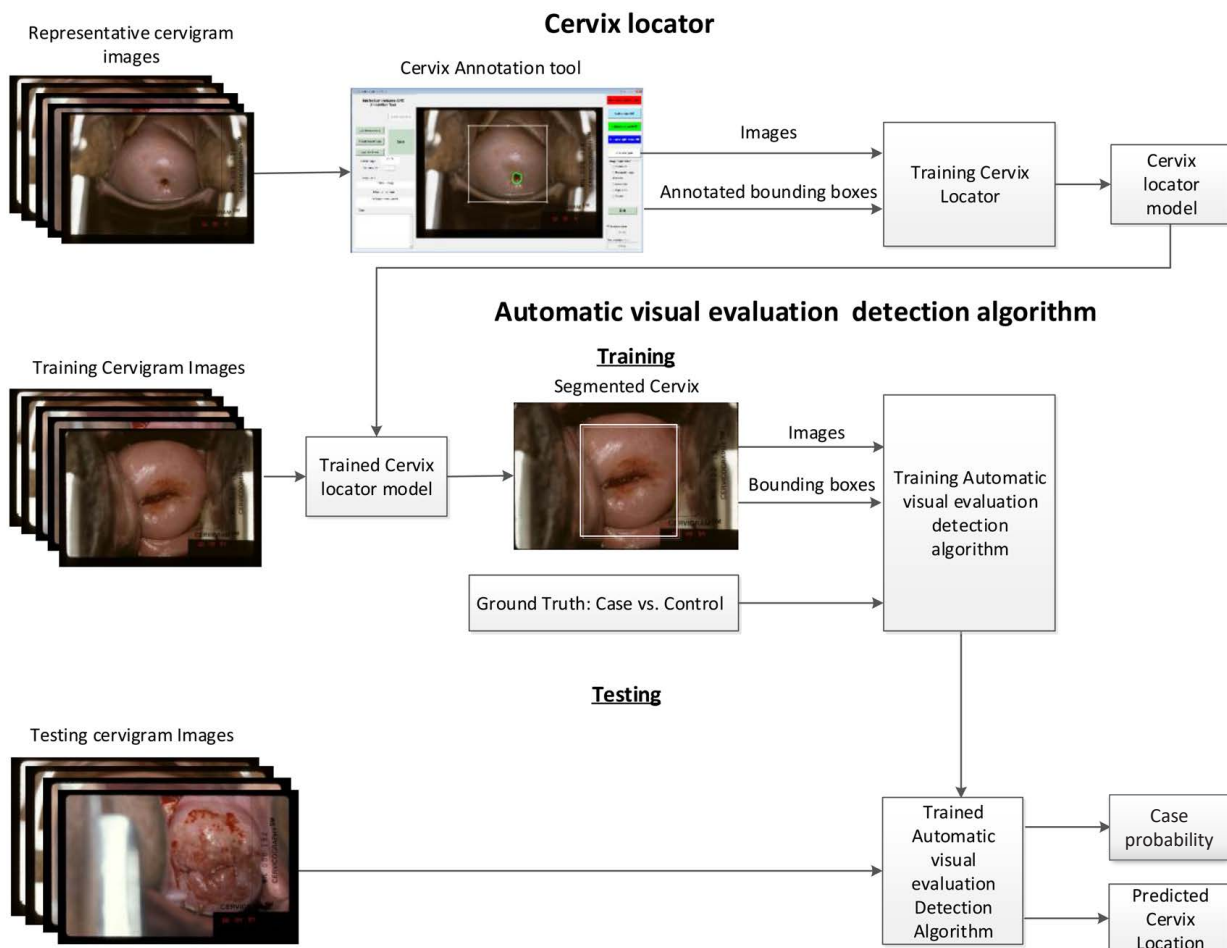
From Hu et al. (2019).

scarcity of accurately labelled medical data, or robust disease end-points, with which to train CNNs for certain medical problems is a challenge to computational analysis. Although large image repositories may be available in some cases, relevant labelling of these images or information about the methods used to determine disease may be unclear or limited, leading to risk of disease misclassification. In addition, the quality of the available images depends on the sophistication of the image-capture system used. However, several specialized techniques (e.g. augmentation, transfer learning) can be used

to address these issues and improve the performance of the model.

(ii)   Performance of method

This technology may be appropriate for both screening and triage of screen-positive women. Early work using deep learning in cervical imagery has been encouraging (Xu et al., 2017). A deep-learning-based object detection method (Ren et al., 2017) was used to develop a visual evaluation algorithm for the detection of cervical precancer. Digitized cervigrams were collected as part of a population-based longitudinal cohort

study in 9406 women in Costa Rica; 241 of the women had histopathological confirmation of precancer (CIN2/3), and 38 had cancer over 7 years of follow-up in 1993–2001 (Hu et al., 2019). Despite limitations in image quality and images without full visualization of the squamocolumnar junction, the algorithm showed high accuracy for the identification of cervical precancers (Fig. 4.10). Automated visual evaluation of cervigrams collected at enrolment identified the cumulative number of cases of precancer or cancer with greater accuracy (AUC, 0.91; 95% CI, 0.89–0.93) than interpretation of the same images by a colposcopist (cervicography; AUC, 0.69; 95% CI, 0.63–0.74; $P < 0.0001$) or conventional cytology (AUC, 0.71; 95% CI = 0.65–0.77; $P < 0.0001$).

AI or deep-learning algorithms may be developed in different ways. Because the discriminative model "reads" images, the image-capture technique is relevant. Using this approach, Xue et al. (2020) developed an algorithm to interpret images captured by the smartphone-based MobileODT system. Automated visual evaluation can classify images of the cervix taken using smartphone camera image-capture systems. Alternatives to this approach include the development of a dedicated high-quality image-capture device that can capture multiple images to mimic a thorough colposcopic evaluation. Such systems can incorporate all the necessary computational power within a single device that is independent of the cloud; this makes them useful in low-resource settings. Both approaches have yet to be evaluated in the field.

(b) Automated cytology technologies

Computer-assisted cytology systems have previously been developed for the reading of conventional or liquid-based cytology slides and are currently used in some settings. For the technical description and performance of these technologies, see Section 4.3.1(c). Recently, new AI-based approaches have been developed for automated evaluation of Pap cytology and dual-stain cytology.

A fully automated approach to evaluate Pap cytology was developed and validated in two studies in the USA. The training and validation data set included 1178 cervical cytology slides from HPV-positive women in Oklahoma who were referred for colposcopy for cytological abnormalities or for treatment of previously diagnosed precancer or cancer. The automated cytology algorithm achieved a performance for detection of CIN2+ (sensitivity, 0.91; specificity, 0.30) similar to that of conventional cytology with a threshold of ASC-US+ (sensitivity, 0.94; specificity, 0.30) (Schiffman et al., 2017). A subsequent study in 1839 HPV-positive women in the KPNC cohort, of whom 310 had precancer (181 with CIN2 and 129 with CIN3/AIS), similarly reported comparability of automated cytology and LBC with a threshold of ASC-US+ and LSIL+ (Yu et al., 2018).

Cytology with p16/Ki-67 dual staining (see Section 4.3.1(e)), which is used as a triage marker for HPV-positive women (see Section 4.4.7), can also be read by an automated system. A CNN deep-learning-based automated algorithm has been developed to evaluate p16/Ki-67 dual-stained slides (CYTOREADER software). The system uses a whole-slide scan followed by a machine-learning algorithm to detect and quantify p16/Ki-67 dual-stain-positive cells. A deep-learning classifier for automated dual-stained slides was compared with manual dual staining and conventional cytology for the detection of precancer in 602 women in Oklahoma who were referred for colposcopy, of whom 53 (8.8%) had CIN3+ (Wentzensen et al., 2021). The automated dual-staining algorithm had marginally lower positivity than manual dual staining (58% vs 63%; $P = 0.06$), with comparable sensitivity for the detection of CIN3+ (automated dual staining: 87%; 95% CI, 76–94%; manual dual staining: 87%; 95% CI, 76–94%; $P = 1.0$) and marginally higher specificity (automated

Fig. 4.10 ROC curve of automated visual evaluation of cervical images, and comparison of performance in identification of CIN2+
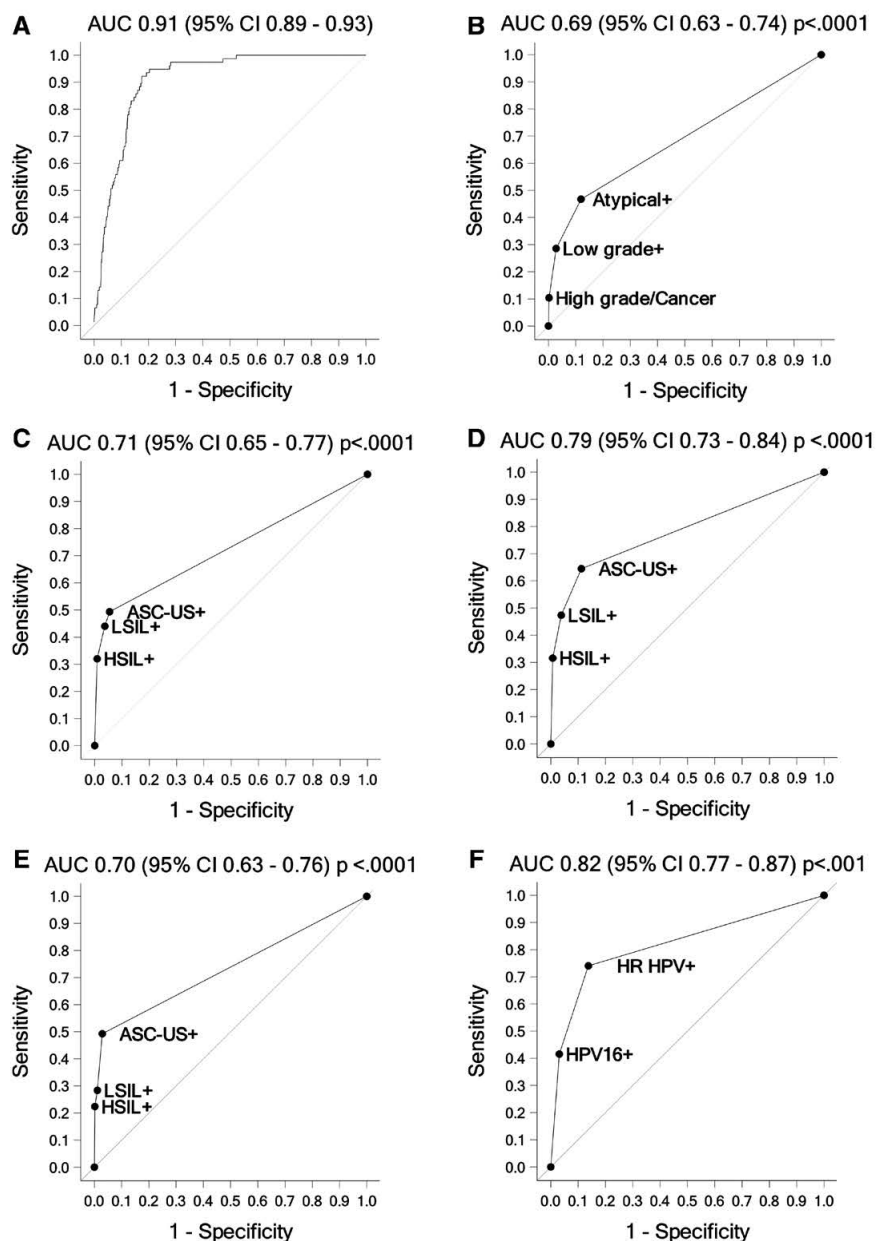
ROC-like curves are shown for the categorical variables for simple visual and statistical comparison with automated visual evaluation (two-sided χ^2 tests). The thresholds are listed on each curve, showing the sensitivity and 1 – specificity applicable to that threshold. Automated visual evaluation was as accurate as or more accurate than all of the screening tests used in the cohort study: (A) automated visual evaluation, (B) cervicography, (C) conventional cytology, (D) liquid-based cytology, (E) first-generation neural network-based cytology, and (F) MY09/MY11 PCR-based hrHPV testing.
ASC-US+. atypical squamous cells of undetermined significance or worse; AUC, area under the curve; CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; HSIL+, high-grade squamous intraepithelial lesion or worse; LSIL+, low-grade squamous intraepithelial lesion or worse; PCR, polymerase chain reaction; ROC, receiver operating characteristic.
From Hu et al. (2019).

dual staining: 46%; 95% CI, 41–51%; manual dual staining: 41%; 95% CI, 36–46%; $P = 0.07$). Similarly, in 3095 HPV-positive women undergoing routine cervical cancer screening in the KPNC cohort, of whom 218 (7.0%) had CIN3+, the test positivity of the automated dual-staining algorithm was significantly lower than that of manual dual staining or conventional cytology with a threshold of ASC-US+ (42%, 50%, and 60%, respectively), with comparable sensitivity (88%, 90%, and 86%, respectively) and higher specificity (62%, 53%, and 42%, respectively). The automated dual-staining algorithm led to a substantial reduction in the colposcopy referral rate compared with conventional cytology, paired with better disease detection, and provided additional risk stratification compared with manual dual staining in HPV-positive women.

4.6.2 Emerging molecular technologies

HPV-based testing may soon replace cytology as the primary screening method for cervical cancer in many parts of the world. However, the lower specificity of HPV DNA-based tests means that some screen-positive women are referred for colposcopy unnecessarily. Novel methods are required to identify which HPV-positive women need to be referred for colposcopy (Cuschieri et al., 2018). Although infection with carcinogenic HPV is necessary for the development of cervical cancer, other molecular changes occur with carcinogenic HPV infection, which result from DNA nucleotide mutations, structural genomic variations, or epigenetic alterations, such as DNA methylation (Steenbergen et al., 2014). Aberrant DNA methylation may help to distinguish non-progressive HPV infections from those that will progress to cervical cancer. It may thus be used as a strategy to triage HPV-positive women.

(a) DNA methylation

(i) Technical description

DNA methylation occurs after the addition of a methyl group to position 5 of the cytosine (C) ring immediately preceding a guanine (G) in the DNA sequence. It occurs mainly at CpG dinucleotide sites (C and G separated by one phosphate), known as CpG islands, which are present in about 60% of human genes (Laird, 2010). Controlled DNA methylation is essential for normal biological processes, such as the regulation of cellular processes including embryonic development, chromosomal instability, and protection from invading foreign viral DNA. However, aberrant DNA methylation can lead to alterations in the functions of gene products that regulate tumour suppression, DNA repair, apoptosis, metastasis, and invasion (Steenbergen et al., 2014; Lorincz, 2016). DNA methylation of some human genes and of the genome of hrHPV genotypes has been shown to be associated with increasing persistence of hrHPV genotypes (Mirabello et al., 2012), precancer (Wentzensen et al., 2009; Bierkens et al., 2013), and invasive cervical cancer (Bowden et al., 2019; Cook et al., 2019; Kelly et al., 2019). DNA methylation of more than 100 human genes and up to 12 carcinogenic HPV genotypes has been evaluated as a possible biomarker for the detection of cervical precancer and cancer using clinician-collected or self-collected cervical samples (Wentzensen et al., 2009; Lorincz, 2016).

(ii) Host DNA methylation

The most widely studied human gene DNA methylation targets have been evaluated as triage tests in HPV-positive women in cross-sectional, case–control, or convenience studies. Most studies evaluated the DNA methylation of the human genes *CADM1*, *MAL*, and *miR-124-2* in different combinations, and of *PAX-1*, *SOX-1*, *POU4F3*, and *FAM19A4*, alone or in combination with *miR-124-2*, for the detection of CIN2+

or CIN3+. Several studies evaluated the DNA methylation of the human gene *EPB41L3*, alone or in combination with DNA methylation of HPV16 (late coding regions L1 and L2), HPV18 (L2), HPV31 (L1), and HPV33 (L2), which is defined as the S5 classifier. The sensitivity and specificity of DNA methylation assays for the detection of prevalent CIN2+ have been shown to vary widely depending on the human gene target, the CpG targets of the gene studied, variations in the thresholds used to define methylation positivity, and the study design (Lorincz, 2016; Kelly et al., 2019).

RCTs comparing detection of CIN2+ in women undergoing testing with DNA methylation compared with cytology, and prospective studies evaluating baseline DNA methylation status to predict the risk of cervical cancer over time have been informative in clarifying the value of DNA methylation as a triage test.

In a non-inferiority RCT (Protection by Offering HPV Testing on Self-Sampled Cervicovaginal Specimens Trial 3 [PROHTECT-3]) in the Netherlands, HPV-positive women registered in the national cervical cancer screening programme who submitted a self-collected sample were randomly allocated to either triage with cytology (509 women) or triage with DNA methylation analysis of the *MAL* and *miR-124-2* genes (515 women) (Verhoef et al., 2014). Detection of CIN2+ with triage by methylation was non-inferior to that by cytology (17% vs 15%; RR, 1.19; 95% CI, 0.90–1.57), and the sensitivity for detection of CIN2+ was equivalent (adjusted sensitivity, 71%; 95% CI, 66–75% for both DNA methylation and cytology), although the sensitivity for detection of CIN3+ was slightly lower with DNA methylation (68%; 95% CI, 63–72%) than with cytology (75%; 95% CI, 70–79%). Also, because of a lower specificity to distinguish < CIN2, referral for colposcopy was more common in the methylation group than in the cytology group (55% vs 29%; *P* < 0.0001) (Verhoef et al., 2014). In a 14-year longitudinal study in 1040 HPV-positive women enrolled in the POBASCAM screening trial in the Netherlands, all of whom underwent testing with DNA methylation and cytology, a negative *FAM19A4/miR-124-2* methylation test indicated lower risk of cervical cancer incidence over a 14-year follow-up period compared with a negative cytology result (< ASC-US) at enrolment (risk ratio, 0.71; 95% CI, 0.16–1.40) (De Strooper et al., 2018).

Previous studies have shown high agreement between clinician-collected and self-collected samples and between lavage-based and brush-based self-collected samples for several human gene DNA methylation targets (Boers et al., 2014; De Strooper et al., 2016); this offers the possibility of conducting screening and triage on the same self-collected specimen.

(iii)   Viral DNA methylation

DNA methylation of the early (E2) and late (L1 and L2) coding regions of the HPV viral genome has been reported to increase with increasing CIN grade for 12 carcinogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (Clarke et al., 2012; Wentzensen et al., 2012; Lorincz et al., 2013; Mirabello et al., 2013; Bowden et al., 2019). The diagnostic accuracy of DNA methylation of HPV genotypes, alone or in various combinations, has been evaluated for detection of CIN2+. In a meta-analysis of seven studies evaluating DNA methylation of the E2, L1, and/or L2 coding regions of HPV16 in HPV16-positive women, the pooled sensitivity for detection of CIN2+ was 74% (95% CI, 57–85%) and the pooled specificity was 73% (95% CI, 66–79%), although there was significant heterogeneity in the observed estimates, because of differences in the CpG sites targeted (Kelly et al., 2019). A second, independent meta-analysis on the diagnostic accuracy of the HPV16 *L1* and/or *L2* genes in 10 studies reported similar findings, with a pooled sensitivity of 77% (95% CI, 63–87%) and a pooled specificity of 64% (95% CI, 55–71%) (Bowden et al., 2019).

The addition of HPV type-specific methylation (HPV types 16, 18, 31, and 33) to a human gene target (*EPB41L3*) as part of the S5 classifier enables testing in all women, irrespective of HPV type positivity. In three studies conducted in HPV-positive women in Canada, Colombia, and the United Kingdom, the sensitivity of the S5 classifier varied from 74% to 82% for detection of CIN2+ and from 84% to 93% for detection of CIN3+, suggesting that the combination of viral and host gene targets may increase detection of CIN2+/CIN3+ (Lorincz et al., 2016; Cook et al., 2019; Ramírez et al., 2021). However, the specificity for < CIN2 varied from 35% to 65%. Compared with either cytology with a threshold of ASC-US+ or HPV16/18 partial genotyping, the S5 classifier had a consistently higher sensitivity for the detection of CIN2+ or CIN3+ but a lower specificity (Lorincz et al., 2016; Cook et al., 2019; Ramírez et al., 2021).

A multiplex DNA methylation test targeting the L1/L2 regions of a wider range of HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) was evaluated in a case–control study in 299 women with precancer (CIN3/AIS) and 360 women who had normal cytology but who were positive for any one of the targeted HPV types (i.e. 30 controls for each of the 12 carcinogenic HPV types evaluated) (Clarke et al., 2018). Methylation was positively associated with CIN3/AIS for all 12 types. The diagnostic accuracy of the 12-type DNA methylation assay was simulated by applying type-specific sensitivity and specificity estimates for the DNA methylation test to a population of 30 000 women using data from a cohort of women undergoing routine cervical screening in the USA. The simulated sensitivity and specificity of the 12-type DNA methylation assay were 80% and 66%, respectively; both were higher than for cytology with a threshold of ASC-US+ (77% and 54%, respectively).

(b) Detection of HPV E6 oncoprotein

Elevated expression of the HPV oncoproteins E6 and E7 is associated with the development of HPV-associated cervical cancer. E6 oncoprotein from HPV16/18/45 can be detected by the Onco*E6* test (Wentzensen et al., 2016). Zhao et al. (2013) reported the test performance when E6 oncoprotein was used as a primary screening method. Another study in China assessed the test performance of E6 oncoprotein for the detection of CIN3+ as triage for HPV-positive women (Qiao et al., 2014). The sensitivity of E6 oncoprotein from HPV16/18/45 was about 50% and the specificity was more than 90% in both clinician-collected and self-collected samples. Compared with HPV16/18/45 DNA testing, the sensitivity was lower but the specificity was higher.

A recent study reported the cumulative incidence of CIN3+ in 1742 women at 10-year follow-up (Dong et al., 2020). The cumulative incidence of CIN3+ was higher in women harbouring methylation at six sites (CpG 5602, 6650, 7034, 7461, 31, and 37) with and without E6 oncoprotein than in women with abnormal cytology. For triage of HPV16-positive women with detection of CIN3+, the sensitivity of E6 oncoprotein was lower than that of cytology (57.1% vs 92.9%), but the specificity was higher (86.5% vs 43.2%). A higher AUC was obtained with the methylation test at the six sites (0.82; 95% CI, 0.69–0.91) than with E6 oncoprotein detection (0.72; 95% CI, 0.58–0.82) and with cytology (0.68; 95% CI, 0.54–0.80).

References

Arbyn M, Ronco G, Cuzick J, Wentzensen N, Castle PE (2009). How to evaluate emerging technologies in cervical cancer screening? *Int J Cancer*. 125(11):2489–96. doi:10.1002/ijc.24774 PMID:19626591

Bierkens M, Hesselink AT, Meijer CJLM, Heideman DAM, Wisman GBA, van der Zee AGJ, et al. (2013). *CADM1* and *MAL* promoter methylation levels in

hrHPV-positive cervical scrapes increase proportional to degree and duration of underlying cervical disease. *Int J Cancer.* 133(6):1293–9. doi:10.1002/ijc.28138 PMID:23456988

Boers A, Bosgraaf RP, van Leeuwen RW, Schuuring E, Heideman DAM, Massuger LFAG, et al. (2014). DNA methylation analysis in self-sampled brush material as a triage test in hrHPV-positive women. *Br J Cancer.* 111(6):1095–101. doi:10.1038/bjc.2014.392 PMID:25032730

Bowden SJ, Kalliala I, Veroniki AA, Arbyn M, Mitra A, Lathouras K, et al. (2019). The use of human papillomavirus DNA methylation in cervical intraepithelial neoplasia: a systematic review and meta-analysis. *EBioMedicine.* 50:246–59. doi:10.1016/j.ebiom.2019.10.053 PMID:31732479

Clarke MA, Gradissimo A, Schiffman M, Lam J, Sollecito CC, Fetterman B, et al. (2018). Human papillomavirus DNA methylation as a biomarker for cervical precancer: consistency across 12 genotypes and potential impact on management of HPV-positive women. *Clin Cancer Res.* 24(9):2194–202. doi:10.1158/1078-0432.CCR-17-3251 PMID:29420222

Clarke MA, Wentzensen N, Mirabello L, Ghosh A, Wacholder S, Harari A, et al. (2012). Human papillomavirus DNA methylation as a potential biomarker for cervical cancer. *Cancer Epidemiol Biomarkers Prev.* 21(12):2125–37. doi:10.1158/1055-9965.EPI-12-0905 PMID:23035178

Cook DA, Krajden M, Brentnall AR, Gondara L, Chan T, Law JH, et al. (2019). Evaluation of a validated methylation triage signature for human papillomavirus positive women in the HPV FOCAL cervical cancer screening trial. *Int J Cancer.* 144(10):2587–95. doi:10.1002/ijc.31976 PMID:30412281

Cuschieri K, Ronco G, Lorincz A, Smith L, Ogilvie G, Mirabello L, et al. (2018). Eurogin roadmap 2017: triage strategies for the management of HPV-positive women in cervical screening programs. *Int J Cancer.* 143(4):735–45. doi:10.1002/ijc.31261 PMID:29341110

De Strooper LMA, Berkhof J, Steenbergen RDM, Lissenberg-Witte BI, Snijders PJF, Meijer CJLM, et al. (2018). Cervical cancer risk in HPV-positive women after a negative *FAM19A4/mir124-2* methylation test: a post hoc analysis in the POBASCAM trial with 14 year follow-up. *Int J Cancer.* 143(6):1541–8. doi:10.1002/ijc.31539 PMID:29663363

De Strooper LMA, Verhoef VMJ, Berkhof J, Hesselink AT, de Bruin HME, van Kemenade FJ, et al. (2016). Validation of the *FAM19A4/mir124-2* DNA methylation test for both lavage- and brush-based self-samples to detect cervical (pre)cancer in HPV-positive women. *Gynecol Oncol.* 141(2):341–7. doi:10.1016/j.ygyno.2016.02.012 PMID:26921784

Dong L, Zhang L, Hu SY, Feng RM, Zhao XL, Zhang Q, et al. (2020). Risk stratification of HPV 16 DNA methylation combined with E6 oncoprotein in cervical cancer screening: a 10-year prospective cohort study. *Clin Epigenetics.* 12(1):62. doi:10.1186/s13148-020-00853-1 PMID:32381054

Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. (2017). Dermatologist-level classification of skin cancer with deep neural networks. *Nature.* 542(7639):115–8. doi:10.1038/nature21056 PMID:28117445

Hu L, Bell D, Antani S, Xue Z, Yu K, Horning MP, et al. (2019). An observational study of deep learning and automated evaluation of cervical images for cancer screening. *J Natl Cancer Inst.* 111(9):923–32. doi:10.1093/jnci/djy225 PMID:30629194

Hussein S, Cao K, Song Q, Bagci U (2017). Risk stratification of lung nodules using 3D CNN-based multi-task learning. In: Niethammer M, Styner M, Aylward S, Zhu H, Oguz I, Yap PT, et al., editors. Information processing in medical imaging. IPMI 2017. (Lecture Notes in Computer Science, Volume 10265). Cham, Switzerland: Springer; pp. 249–60. doi:10.1007/978-3-319-59050-9_20

Islam MT, Aowal MA, Tahseen Minhaz A, Ashraf K (2017). Abnormality detection and localization in chest X-rays using deep convolutional neural networks. Ithaca (NY), USA: Cornell University. Available from: https://arxiv.org/pdf/1705.09850.pdf.

Kelly H, Benavente Y, Pavon MA, De Sanjose S, Mayaud P, Lorincz AT (2019). Performance of DNA methylation assays for detection of high-grade cervical intraepithelial neoplasia (CIN2+): a systematic review and meta-analysis. *Br J Cancer.* 121(11):954–65. doi:10.1038/s41416-019-0593-4 PMID:31616037

Laird PW (2010). Principles and challenges of genome-wide DNA methylation analysis. *Nat Rev Genet.* 11(3):191–203. doi:10.1038/nrg2732 PMID:20125086

Lorincz AT (2016). Virtues and weaknesses of DNA methylation as a test for cervical cancer prevention. *Acta Cytol.* 60(6):501–12. doi:10.1159/000450595 PMID:27806357

Lorincz AT, Brentnall AR, Scibior-Bentkowska D, Reuter C, Banwait R, Cadman L, et al. (2016). Validation of a DNA methylation HPV triage classifier in a screening sample. *Int J Cancer.* 138(11):2745–51. doi:10.1002/ijc.30008 PMID:26790008

Lorincz AT, Brentnall AR, Vasiljević N, Scibior-Bentkowska D, Castanon A, Fiander A, et al. (2013). HPV16 L1 and L2 DNA methylation predicts high-grade cervical intraepithelial neoplasia in women with mildly abnormal cervical cytology. *Int J Cancer.* 133(3):637–44. doi:10.1002/ijc.28050 PMID:23335178

McKinney SM, Sieniek M, Godbole V, Godwin J, Antropova N, Ashrafian H, et al. (2020). International evaluation of an AI system for breast cancer screening.

Nature. 577(7788):89–94. doi:10.1038/s41586-019-1799-6 PMID:31894144

Mirabello L, Schiffman M, Ghosh A, Rodriguez AC, Vasiljevic N, Wentzensen N, et al. (2013). Elevated methylation of HPV16 DNA is associated with the development of high grade cervical intraepithelial neoplasia. *Int J Cancer.* 132(6):1412–22. doi:10.1002/ijc.27750 PMID:22847263

Mirabello L, Sun C, Ghosh A, Rodriguez AC, Schiffman M, Wentzensen N, et al. (2012). Methylation of human papillomavirus type 16 genome and risk of cervical precancer in a Costa Rican population. *J Natl Cancer Inst.* 104(7):556–65. doi:10.1093/jnci/djs135 PMID:22448030

Qiao YL, Jeronimo J, Zhao FH, Schweizer J, Chen W, Valdez M, et al. (2014). Lower cost strategies for triage of human papillomavirus DNA-positive women. *Int J Cancer.* 134(12):2891–901. doi:10.1002/ijc.28616 PMID:24248915

Ramírez AT, Sánchez GI, Nedjai B, Agudelo MC, Brentnall AR, Cuschieri K, et al.; ASC-US-COL Trial Group (2021). Effective methylation triage of HPV positive women with abnormal cytology in a middle-income country. *Int J Cancer.* 148(6):1383–93. doi:10.1002/ijc.33314 PMID:33006394

Ren S, He K, Girshick R, Sun J (2017). Faster R-CNN: towards real-time object detection with region proposal networks. *IEEE Trans Pattern Anal Mach Intell.* 39(6):1137–49. doi:10.1109/TPAMI.2016.2577031 PMID:27295650

Schiffman M, Yu K, Zuna R, Terence Dunn S, Zhang H, Walker J, et al. (2017). Proof-of-principle study of a novel cervical screening and triage strategy: computer-analyzed cytology to decide which HPV-positive women are likely to have ≥CIN2. *Int J Cancer.* 140(3):718–25. doi:10.1002/ijc.30456 PMID:27696414

Steenbergen RDM, Snijders PJF, Heideman DAM, Meijer CJLM (2014). Clinical implications of (epi)genetic changes in HPV-induced cervical precancerous lesions. *Nat Rev Cancer.* 14(6):395–405. doi:10.1038/nrc3728 PMID:24854082

Ting DSW, Cheung CYL, Lim G, Tan GSW, Quang ND, Gan A, et al. (2017). Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multi-ethnic populations with diabetes. *JAMA.* 318(22):2211–23. doi:10.1001/jama.2017.18152 PMID:29234807

Verhoef VMJ, Bosgraaf RP, van Kemenade FJ, Rozendaal L, Heideman DAM, Hesselink AT, et al. (2014). Triage by methylation-marker testing versus cytology in women who test HPV-positive on self-collected cervicovaginal specimens (PROHTECT-3): a randomised controlled non-inferiority trial. *Lancet Oncol.* 15(3):315–22. doi:10.1016/S1470-2045(14)70019-1 PMID:24529697

Wei JW, Suriawinata AA, Vaickus LJ, Ren B, Liu X, Lisovsky M, et al. (2020). Evaluation of a deep neural network for automated classification of colorectal polyps on histopathologic slides. *JAMA Netw Open.* 3(4):e203398. doi:10.1001/jamanetworkopen.2020.3398 PMID:32324237

Wentzensen N, Lahrmann B, Clarke MA, Kinney W, Tokugawa D, Poitras N, et al. (2021). Accuracy and efficiency of deep-learning-based automation of dual stain cytology in cervical cancer screening. *J Natl Cancer Inst.* 113(1):72–9. doi:10.1093/jnci/djaa066 PMID:32584382

Wentzensen N, Schiffman M, Palmer T, Arbyn M (2016). Triage of HPV positive women in cervical cancer screening. *J Clin Virol.* 76(Suppl 1):S49–55. doi:10.1016/j.jcv.2015.11.015 PMID:26643050

Wentzensen N, Sherman ME, Schiffman M, Wang SS (2009). Utility of methylation markers in cervical cancer early detection: appraisal of the state-of-the-science. *Gynecol Oncol.* 112(2):293–9. doi:10.1016/j.ygyno.2008.10.012 PMID:19054549

Wentzensen N, Silver MI (2016). Biomarkers for cervical cancer prevention programs: the long and winding road from discovery to clinical use. *J Low Genit Tract Dis.* 20(3):191–4. doi:10.1097/LGT.0000000000000231 PMID:27243141

Wentzensen N, Sun C, Ghosh A, Kinney W, Mirabello L, Wacholder S, et al. (2012). Methylation of HPV18, HPV31, and HPV45 genomes and cervical intraepithelial neoplasia grade 3. *J Natl Cancer Inst.* 104(22):1738–49. doi:10.1093/jnci/djs425 PMID:23093560

Wentzensen N, Wacholder S (2013). From differences in means between cases and controls to risk stratification: a business plan for biomarker development. *Cancer Discov.* 3(2):148–57. doi:10.1158/2159-8290.CD-12-0196 PMID:23299199

Xu T, Zhang H, Xin C, Kim E, Long LR, Xue Z, et al. (2017). Multi-feature based benchmark for cervical dysplasia classification evaluation. *Pattern Recognit.* 63:468–75. doi:10.1016/j.patcog.2016.09.027 PMID:28603299

Xue Z, Novetsky AP, Einstein MH, Marcus JZ, Befano B, Guo P, et al. (2020). A demonstration of automated visual evaluation of cervical images taken with a smartphone camera. *Int J Cancer.* 147(9):2416–23. doi:10.1002/ijc.33029 PMID:32356305

Yu K, Hyun N, Fetterman B, Lorey T, Raine-Bennett TR, Zhang H, et al. (2018). Automated cervical screening and triage, based on HPV testing and computer-interpreted cytology. *J Natl Cancer Inst.* 110(11):1222–8. doi:10.1093/jnci/djy044 PMID:29659930

Zhao FH, Jeronimo J, Qiao YL, Schweizer J, Chen W, Valdez M, et al. (2013). An evaluation of novel, lower-cost molecular screening tests for human papillomavirus in rural China. *Cancer Prev Res (Phila).* 6(9):938–48. doi:10.1158/1940-6207.CAPR-13-0091 PMID:23878179

5. SCREEN-AND-TREAT APPROACH AND WOMEN AT DIFFERENTIAL RISK

5.1 Screen-and-treat approach

The primary aim of cervical cancer screening is to identify women with cervical precancerous lesions that need to be treated to prevent invasion (Schiffman et al., 2016; Wentzensen et al., 2017). Although cervical screening involves the whole population of women over a wide age range, only very few women actually need treatment. Many cervical cancer screening programmes rely on a multistep process to achieve efficient cervical cancer prevention, including an initial screening test with or without triage testing, colposcopic evaluation with cervical biopsies, and treatment decisions based on histological evaluation of cervical biopsies, followed by removal or destruction of the transformation zone, including the precancerous tissue (Arbyn et al., 2010; Perkins et al., 2020). This approach enables treatment to be limited to women with a very high probability of an existing precancer, and avoids overtreatment of women without precancer. A few guidelines in multistep screening programmes recommend immediate treatment without histological confirmation in women with a very high probability of an existing precancer, as indicated by screening and triage tests (Perkins et al., 2020). Before treatment, all women with a positive screening test result should undergo visual evaluation to assess the lesion size and the type of the transformation zone and to rule out suspected invasive cancer (WHO, 2011, 2014, 2019).

5.1.1 Rationale for screen-and-treat strategies

Multistep cervical cancer screening programmes involving colposcopy and histology require considerable investment in infrastructure, training of a skilled workforce, and quality control efforts (Arbyn et al., 2010). These programmes have typically been developed over decades and are difficult to establish in resource-constrained settings. Furthermore, multistep cervical cancer screening strategies require multiple visits with patient–provider interactions, including visits for screening, surveillance, colposcopy, and treatment. At each step there is a risk of loss to follow-up, with the consequence that a prevalent precancer may progress to cancer if left untreated. Loss to follow-up is a particular concern in resource-constrained settings, where women may have to travel long distances to health facilities and cannot be easily contacted to communicate test results and invite them to return for follow-up visits and treatment if needed. Loss to

follow-up can be decreased when fewer visits to a clinic are required, and it is minimized when screening and treatment are performed during the same visit.

Screen-and-treat approaches are designed to require fewer resources compared with multistep programmes, and to decrease the need for repeat visits (Denny et al., 2017; Cherniak et al., 2019). Although different screen-and-treat strategies exist, the unifying feature is that treatment is performed without a colposcopy-directed biopsy and histological confirmation of precancer. Typically, in screen-and-treat programmes more women need to undergo treatment than in multistep screening programmes, in which the positive predictive value (PPV) increases at each step. A variation of the screen-and-treat approach is the screen-triage-and-treat strategy, known as the see-and-treat strategy when colposcopy triage is used, in which screen-positive women undergo a second test to increase the specificity and PPV for precancer, to decrease unnecessary treatment.

Ideally, screening and triage tests should be performed with a fast turnaround, to enable both screening and treatment to be carried out during a single visit. In some settings, delayed processing of screening tests may be the only option and may require women to return for treatment.

5.1.2 Screening and triage modalities in screen-and-treat programmes

The screening modalities used in screen-and-treat programmes are either visual tests, such as visual inspection with acetic acid (VIA) and automated visual evaluation, or molecular tests, such as human papillomavirus (HPV) testing with or without genotyping. See-and-treat strategies include colposcopic evaluation before treatment. Because cytology involves delayed processing and requires substantial infrastructure and training, it is not suitable for screen-and-treat programmes. Accuracy data and effectiveness

studies of the underlying screening tests outside of screen-and-treat programmes are summarized elsewhere (see Section 4.2, Section 4.4, and Section 1.2.5).

(a) Visual inspection with acetic acid (VIA)

VIA was the first screening approach used in screen-and-treat programmes. VIA is a very simple and low-cost screening approach, which is conducted by applying acetic acid to the cervix, followed by visual inspection and assessment of acetowhitening (see Section 4.2.1).

The advantages of VIA are its wide availability, the lack of infrastructure requirements, and the possibility of making immediate treatment decisions and performing treatment in the same session. However, despite its appeal as a simple test, VIA requires training and quality control; it is also a highly subjective and variable test that has low accuracy. Any screen-and-treat strategy requires visual evaluation of the cervix to determine eligibility for treatment by either ablation or incision; assessment of eligibility for treatment is part of the visual evaluation performed for VIA.

(b) Automated visual evaluation

Recently, automated approaches have been developed to provide objective evaluation of cervical images (see Section 4.6.1).

Although automated visual evaluation has shown good performance in primary screening, it requires a health worker to take a high-quality image in the entire screening population. Alternatively, automated visual evaluation can be used as a triage test for women with positive HPV test results from self-collected samples; this dramatically decreases the number of women for whom automated visual evaluation is needed. This approach may enable the implementation of single-visit screen-and-treat strategies in the future, which would decrease the proportion of women who need treatment compared with VIA-and-treat or HPV test-and-treat strategies.

(c) HPV testing

HPV testing is an objective test that has higher accuracy for the detection of precancer compared with VIA (see Section 4.4.3).

The turnaround time for HPV tests is important for the implementation of screen-and-treat approaches. When HPV testing is not performed immediately, women need to be contacted to communicate test results and screen-positive women need to return to the clinic for treatment. However, rapid HPV testing, or point-of-care testing, which can be performed in clinics where women undergo screening, is possible and enables the implementation of single-visit strategies similar to those of VIA programmes.

5.1.3 Treatment modalities in screen-and-treat programmes

Treatment of cervical cancer and of precancerous lesions as commonly performed in organized screening programmes is described in Section 1.2.5.

(a) Ablative treatment

Ablative treatment approaches, such as cryotherapy and thermal ablation, are based on the destruction of the tissue at risk, without tissue excision. Ablative treatment is efficacious for ectocervical lesions, but endocervical lesions cannot be treated efficiently using this method. In addition, in postmenopausal women the transformation zone is located in the endocervical canal and cannot be reached with ablative treatment modalities.

The most widely evaluated screen-and-treat strategy is the combination of VIA with cryotherapy. This approach can be conducted in a single visit by a health worker who performs the screening, evaluates eligibility for treatment, and then performs cryotherapy. Cryotherapy uses gas (typically carbon dioxide or nitrous oxide) to cool down a metallic probe to −90 °C; this probe is applied to the surface of the cervix for topical tissue destruction. A reliable supply of gas can be a challenge in resource-constrained settings, and this has led to the failure of cryotherapy programmes in some settings (Maza et al., 2018). Cryotherapy was shown low recurrence rates with limited harms, but with low-quality evidence, which limits the assessments of efficacy and harms (Chamot et al., 2010; Santesso et al., 2016).

Recently, thermal ablation has been evaluated as an alternative to cryotherapy. Thermal ablation is based on the application of a heated probe to the surface of the cervix for topical tissue destruction. Thermal ablation does not require gas and can be performed with a hand-held battery-powered device; this decreases the infrastructure requirements compared with cryotherapy. Several studies have suggested that thermal ablation has a performance comparable to that of cryotherapy, and that it is safe and acceptable (Dolman et al., 2014; Randall et al., 2019; Sandoval et al., 2019; Pinder et al., 2020; Zhao et al., 2020). In 2019, WHO published evidence-based guidelines on the use of thermal ablation to treat cervical precancer (WHO, 2019).

(b) Excisional treatment

In some settings, excisional treatment has been used as the primary treatment modality in screen-and-treat programmes (Chamot et al., 2010; Santesso et al., 2016; Greene et al., 2019). Excisional treatment using electrical loops or surgical knives requires more infrastructure in clinics and providers who are trained and experienced. Tissue specimens that are removed with excisional treatment can be used for histological evaluation to confirm the presence of cervical precancer and to rule out invasive cancer. Although establishing an infrastructure for excisional treatment on a large scale is challenging in resource-constrained settings, excisional treatment needs to be available for women who are not eligible for ablative treatment.

5.1.4 Evaluation of screen-and-treat strategies

Evaluation of the efficacy, benefits, and harms of screen-and-treat strategies requires different study designs compared with strategies that rely on colposcopy-directed biopsy with histological confirmation and excisional treatment. Large screening trials have evaluated the detection of cervical precancer and cancer at baseline and the detection of precancer in the second screening round as indicators of screening efficacy. These evaluations require histological end-points, which are not available in screen-and-treat strategies. When no histological information is available, the effects of screen-and-treat strategies can be evaluated only by using population-wide estimates of cancer incidence. However, in low-resource settings cancer registries are often either non-existent or unreliable, and substantial lead time is needed to observe a reduction in cancer incidence. Therefore, clinical trials evaluating screen-and-treat strategies usually include a histology component, with biopsy sampling at the time of ablative treatment and/or during follow-up after treatment.

Screen-and-treat strategies typically lead to the treatment of a larger proportion of the screened population compared with multistep screening strategies, treating many women without prevalent precancer. Therefore, assessment of treatment harms plays a greater role compared with strategies in which treatment is restricted to women with histological confirmation of precancer.

Ten studies reported on the effectiveness of screen-and-treat strategies to prevent precancerous lesions or cervical cancer (Table 5.1). The screening modality included VIA in seven studies and HPV DNA testing in two studies, and VIA and HPV DNA testing were compared in one randomized controlled trial (RCT). The treatment modalities used in women with a positive screening test result in these studies included cryotherapy in seven studies, a combination of cryotherapy and thermal ablation in two studies, and thermal ablation in one study.

In a large RCT in South Africa, 6555 women (5001 HIV-negative women, 784 women living with HIV [WLHIV], and 770 women of unknown status) were randomized into three groups: to receive cryotherapy if an HPV DNA test result was positive, to receive cryotherapy if a VIA test result was positive, or to undergo delayed evaluation (Denny et al., 2005). All women underwent colposcopy and biopsy of all acetowhite lesions after 6 months or 12 months to ascertain cervical intraepithelial neoplasia grade 2 or worse (CIN2+) end-points. In both the HPV DNA test screening arm and the VIA screening arm, 22% of women were referred for treatment with cryotherapy. In an analysis restricted to the HIV-negative women at the 6-month visit, CIN2+ was diagnosed in 0.85% (95% confidence interval [CI], 0.40–1.29%) of the women screened with HPV DNA testing, 2.11% (95% CI, 1.42–2.79%) of the women screened with VIA, and 2.75% (95% CI, 1.96–3.54%) of the women in the delayed evaluation group. Over 12 months, an HPV screen-and-treat protocol would have led to a 56% reduction in the prevalence of CIN2+, whereas a VIA screen-and-treat protocol would have led to a 27% reduction in the prevalence of CIN2+ compared with the delayed evaluation group (Denny et al., 2005). In both treatment groups, 36% of women reported pain or light-headedness during the procedure. Vaginal discharge was common after cryotherapy, and abdominal pain occurred in a few women, but serious adverse events were very rare. There was a significant reduction in the cumulative prevalence of CIN2+ in the HPV DNA testing arm compared with the delayed evaluation arm (1.4% vs 4.6%; relative risk [RR], 0.31; 95% CI, 0.20–0.50), but there was no significant reduction in the VIA arm compared with the delayed evaluation arm (3.5% vs 4.6%; RR, 0.76; 95% CI, 0.52–1.1). In WLHIV, similar reductions in the

Table 5.1 Studies on the effectiveness of screen-and-treat strategies for the prevention of HSIL+/CIN2+

Reference Design Country	Pathway/ comparison	Screened population size Age (years) HIV prevalence	Sample and test Screen positivity (%)	Number of visits Treatment	Follow-up time Follow-up population	Ascertainment of end-points	Summary findings
Denny et al. (2005) RCT South Africa	VIA + treatment vs HPV + treatment vs delayed evaluation	6555 35–65 12% (782 HIV-positive of 6542 results)	Cervical specimen on HC2 VIA positivity: 22 HPV positivity: 22	2 Cryotherapy	6 mo and 12 mo 5667	Colposcopy and biopsy	6 mo: CIN2+ prevalence (95% CI): HPV DNA group: 0.80% (0.4–1.2%) VIA group: 2.23% (1.57–2.89%) Control group: 3.55% (2.71–4.39%) 12 mo: CIN2+ prevalence (95% CI): HPV DNA group: 1.42% (0.88–1.97%) VIA group: 2.91% (2.12% – 3.69%) Control group: 5.41% (4.32–6.5%)
Sankaranarayanan et al. (2007) Prospective cohort India	VIA (+ colposcopy + biopsies) + treatment	1879 30–59 NR	NA NR	1 Cryotherapy	6 mo 1026 (treated with cryotherapy at enrolment)	Histology or colposcopy	CIN2+: 2.04% Invasive cancer: 0.2% Cure rates: 71.4% for women with CIN2 and 68.0% for women with CIN3

Table 5.1   (continued)

Reference Design Country	Pathway/ comparison	Screened population size Age (years) HIV prevalence	Sample and test Screen positivity (%)	Number of visits Treatment	Follow-up time Follow-up population	Ascertainment of end-points	Summary findings
Parham et al. (2010) Prospective cohort Zambia	VIA-DC	6572 33 (median age) 100%	NA VIA positivity: 54	1 where possible Cryotherapy	20% of women who underwent treatment returned for FU at 6–12 mo NA	Estimation of cervical cancer deaths prevented	58.5% of VIA-positive women were eligible for ablative treatment 1 cervical cancer death was prevented per 46 WLHIV screened using the screen-and-treat programme 34% of women who underwent cryotherapy had abnormal VIA test result at 6 mo (34% of them had CIN2+) 68% of women who underwent LEEP had abnormal VIA test result at 6 mo (40% of them had CIN2+)
Martin et al. (2014) Prospective cohort Guyana	VIA + treatment	21 597 25–49 8%	NA VIA positivity: 13 WLHIV: 16 HIV-negative women: 13	1 Cryotherapy	12 mo 1027 of 2046 VIA-positive at baseline (69% of WLHIV screened vs 48% HIV-negative/ unknown screened)	VIA	85% of women who were eligible received immediate cryotherapy 95% of women were VIA-negative at second screening Non-physician providers were more likely than physicians to continue offering services
Starks et al. (2014) Prospective cohort Mexico	HPV + treatment	2522 30–50 NR	Vaginal sample on HC2 HPV positivity: 20	NR Cryotherapy	6 mo and 2 yr for women treated with cryotherapy 226 at 6 mo 137 at 2 yr (of 291 women treated with cryotherapy)	6 mo: HPV + VIA + colposcopy + biopsy 2 yr: HPV + VIA + colposcopy + biopsy	VIA false-positive rate: 5% At 6-mo FU, 68% women were hrHPV-negative Of 32% ($n = 73$) hrHPV-positive: 5 CIN2+ At 2-yr FU, 85% of women were hrHPV-negative Of 15% ($n = 21$) hrHPV-positive: 0 CIN2+

Table 5.1 (continued)

Reference Design Country	Pathway/ comparison	Screened population size Age (years) HIV prevalence	Sample and test Screen positivity (%)	Number of visits Treatment	Follow-up time Follow-up population	Ascertainment of end-points	Summary findings
Thida et al. (2015) Community-based evaluation study Myanmar	VIA + treatment	1617 30–49 Known HIV-positive cases and those with other gynaecological problems were referred for further management	NA VIA positivity: 7.5	1 Cryotherapy	12 mo 103 of 119 (treated with cryotherapy at enrolment)	VIA	Treatment rate: 98.4% FU: 3 women with persistent lesions Cure rate: 97.1%
Chigbu et al. (2017) Prospective cohort Nigeria	VIA + treatment	653 30–50 NR	NA VIA positivity: 10.9	1 Cryotherapy	12 mo 649	VIA (by same provider) + biopsies (if VIA-positive)	HSIL at enrolment: 4.1% HSIL at 1 yr: 0.5% (reduction statistically significant; $P = 0.0001$) Cryotherapy cure rate: 87.9% (95% CI, 76.82–94.33%)
Tran et al. (2017) Prospective cohort Cameroon	"HPV16/18/45-positive" or "positive to other hrHPV + VIA/VILI abnormal" + treatment	1012 30–49 NR	Vaginal sample on Xpert HPV test hrHPV prevalence: 18.6 HPV16/18/45 positivity: 6 Other hrHPV + VIA/VILI: 6	1 Thermal ablation	6 mo and 12 mo 130 at 6 mo 112 at 12 mo	Persistence of high-grade disease on cytology	At baseline, treatment of < CIN2 (overtreatment): 9.9% At 6 mo, 89% had no evidence of disease Cure rate[a]: 58.8% At 12 mo, 87% had no evidence of disease Cure rate[a]: 70.6% Treatment failure (higher risk of persistent disease) was associated with the presence of occult endocervical lesions at baseline diagnosis

Table 5.1 (continued)

Reference Design Country	Pathway/ comparison	Screened population size Age (years) HIV prevalence	Sample and test Screen positivity (%)	Number of visits Treatment	Follow-up time Follow-up population	Ascertainment of end-points	Summary findings
Cholli et al. (2018) Prospective cohort Cameroon	VIA/VILI-DC hrHPV testing (for research purposes)	913 ≥ 30 42%	Cervical specimen on *care*HPV test VIA/VILI-DC positivity: 4.8 WLHIV: 7.6 HIV-negative women: 2.8 hrHPV positivity: 24.4 WLHIV: 41 HIV-negative women: 12	1 Cryotherapy Thermal ablation	12 mo 136 of 245 (positive for VIA/VILI-DC and/or hrHPV)	VIA/VILI-DC + hrHPV testing (co-testing)	50% of VIA/VILI-DC-positive women were hrHPV-negative VIA/VILI-DC-positive women with HIV infection were 3 times as likely to be hrHPV-positive than HIV-negative women (65% vs 20%) FU: 49% of women who were HPV-positive at enrolment retested negative (44% cleared infection without treatment)
Pinder et al. (2020) RCT (pilot phase) Zambia	VIA + treatment (VIA-positive women randomized to thermal ablation or cryotherapy or LLETZ) (HPV testing for research purposes)	NR ≥ 25 52%	Cervical specimen on Xpert HPV test NR	1 Thermal ablation vs cryotherapy vs LLETZ	6 mo 750	VIA + HPV testing (participants who were VIA-negative but HPV-positive were advised to attend a repeat FU visit at 12 mo)	Treatment success (*P* = 0.31): Cryotherapy: 60% Thermal ablation: 64% LLETZ: 67% Few participants reported moderate to severe pain in any group immediately after the procedure None of the participants reported any complication requiring medical consultation or admission to hospital

CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; FU, follow-up; HC2, Hybrid Capture 2; HPV, human papillomavirus; hrHPV, high-risk HPV; HSIL, high-grade squamous intraepithelial lesion; LEEP; loop electrosurgical excision procedure; LLETZ, large loop excision of the transformation zone; mo, month or months; NA, not applicable; NR, not reported; RCT, randomized controlled trial; VIA, visual inspection with acetic acid; VIA-DC, VIA enhanced by digital cervicography; VIA/VILI, visual inspection with acetic acid and Lugol's iodine; VILI-DC, visual inspection with Lugol's iodine enhanced by digital cervicography; WLHIV, women living with HIV; yr, year or years.

[a] In women with CIN2+ disease at enrolment who underwent thermal ablation (*n* = 17).

cumulative prevalence of CIN2+ over 36 months were observed in the HPV DNA testing arm compared with the delayed evaluation arm (3.1% vs 15.5%; RR, 0.20; 95% CI, 0.06–0.69), and to a lesser extent in the VIA arm (7.6%; RR, 0.51; 95% CI, 0.29–0.89) (Kuhn et al., 2010) (see also Section 5.2.1).

The observational studies on VIA screen-and-treat approaches reported a wide range of test positivity, ranging from 5% to 22%, and in HPV screen-and-treat studies the test positivity ranged from 19% to 24% (Table 5.1). Several studies included WLHIV, with variable proportions ranging from 8% to 100%. Test positivity was higher for both VIA and HPV testing in WLHIV compared with HIV-negative women. The assessment of treatment success was heterogeneous; some studies used biopsy-confirmed end-points at different time points, in part triggered by positive VIA test results in follow-up, whereas other studies accepted a negative VIA result on follow-up examination as an indicator of treatment success. [This limited the comparability of treatment success across studies.]

In a study of VIA and cryotherapy in 653 women in Nigeria (Chigbu et al., 2017), the cure rate was reported to be 88% at a follow-up of 1 year. However, follow-up biopsy and histological confirmation was obtained only from women with a persistent positive VIA test result or a new positive VIA test result at 1 year. [This possibly inflates the estimate.] In a study of a screen-and-treat strategy in 1012 women in Cameroon (Tran et al., 2017), women with positive test results for HPV16, HPV18, HPV45, or other carcinogenic types and abnormal VIA results were treated using thermal ablation. A cure rate of 71% at 12 months was reported. [Follow-up diagnosis was based on cytology, not histologically verified CIN.]

Several studies did not report the initial test positivity, and others did not have enough case numbers to assess treatment success.

5.2 Screening of women at differential risk

5.2.1 Screening of women living with HIV

Based on the most recent report, in 2019 an estimated 36.2 million people aged 15 years or older were living with HIV, 53% of whom were women (UNAIDS, 2020). Fig. 5.1 shows the prevalence of HIV infection in the global population by country (Roser & Ritchie, 2019). There are significant differences between world regions: sub-Saharan Africa has the highest number of WLHIV (15.1 million), and 64% (12.3 million) of all WLHIV live in countries in eastern and southern Africa (UNAIDS, 2020); this is also the region with the highest age-standardized incidence rates of invasive cervical cancer (ICC) (Bray et al., 2018). In 2018, 569 478 incident cases of ICC were reported worldwide, and an estimated 33 000 of those cases (5.8%; 95% CI, 4.3–7.6%) were in WLHIV (Stelzle et al., 2021). The fraction of cervical cancer cases attributable to HIV varies dramatically according to region and is highest in eastern and southern Africa, where more than 29.7% of cases of cervical cancer can be attributed to HIV (Stelzle et al., 2021).

After significant advances in the treatment of HIV infection with antiretroviral therapy (ART) and the worldwide use of treatment-as-prevention measures, a reduction in HIV-associated mortality was observed in the past decade, resulting in an increase in HIV prevalence as people with HIV survived longer on ART. Longer survival times in WLHIV may be associated with an increase in the incidence of cervical cancer, because WLHIV remain susceptible to the acquisition and persistence of carcinogenic HPV infections and the incidence and progression of cervical lesions. Compared with HIV-negative women, WLHIV have an increased risk of acquisition and persistence of carcinogenic HPV infections (Looker et al., 2018).

(a) Natural history of HPV infection in WLHIV

(i) Association between HIV and HPV

Compared with HIV-negative women, WLHIV are more likely to acquire carcinogenic HPV infections (adjusted RR, 2.18; 95% CI, 1.58–3.01), are less likely to clear carcinogenic HPV infections (adjusted RR, 0.71; 95% CI, 0.58–0.91), and are more likely to be infected with multiple carcinogenic HPV types (Looker et al., 2018) (see Section 1.2.2). HPV can also act as a cofactor of HIV acquisition (Looker et al., 2018), and WLHIV have high rates of co-infection with HPV because the risk profiles for acquisition of HIV and HPV are similar. Furthermore, both HIV and HPV infections elicit and thrive on viral and host factors that impair the immune system.

(ii) Association between HIV and progression of HSIL to ICC

WLHIV have a 2–5-fold higher incidence of high-grade squamous intraepithelial lesion (HSIL) and a 4-fold higher incidence of ICC compared with HIV-negative women (De Vuyst et al., 2008; Denslow et al., 2014; Liu et al., 2018). Case reports on the rapid progression of HSIL to ICC in WLHIV (Rellihan et al., 1990; Saccucci et al., 1996; Holcomb et al., 1998) were published before the wide availability of ART. Starting in 1993, the United States Centers for Disease Control and Prevention (CDC, 1992) and the European Commission (Ancelle-Park et al., 1993) classified ICC as an AIDS-defining illness. WLHIV have an increased risk of developing ICC 7–15 years earlier than HIV-negative women (Gichangi et al., 2003; van Aardt et al., 2015; Rudd et al., 2017; Awolude & Oyerinde, 2018; Trejo et al., 2020), and WLHIV more frequently present with poorly differentiated tumours and more advanced disease with poorer prognosis (Moodley, et al., 2001; Dryden-Peterson et al., 2016) (see Section 1.2.2).

(iii) Association between ART and the natural history of HPV, SIL, and ICC in WLHIV

In 2015, WHO issued new guidelines on when to start ART, which recommended that all people living with HIV should start ART as soon as HIV infection is confirmed, irrespective of the CD4+ T-cell count (WHO, 2015).

A systematic review and meta-analysis that assessed the interactions between ART, carcinogenic HPV infections, and cervical lesions in WLHIV found that WLHIV taking ART had a lower prevalence of carcinogenic HPV infections compared with those not taking ART (adjusted odds ratio [OR], 0.83; 95% CI, 0.70–0.99) (Kelly et al., 2018). WLHIV taking ART had a lower incidence of HSIL or worse (HSIL+) (adjusted OR, 0.59, 95% CI, 0.40–0.87), a lower risk of SIL progression (adjusted hazard ratio [HR], 0.64; 95% CI, 0.54–0.75), a higher likelihood of SIL regression (adjusted HR, 1.54; 95% CI, 1.30–1.82), and a lower incidence of ICC (crude HR, 0.40; 95% CI, 0.18–0.87) compared with those not taking ART (Kelly et al., 2018). The greatest reductions were observed in women taking ART for a prolonged duration with sustained HIV viral suppression and in women initiating ART at a high CD4+ cell count. [A limitation acknowledged in the review is that most studies used a binary category of ART users and ART-naive women and few evaluated the effect of ART duration or ART use with prolonged HIV viral suppression. This limits the comparability in women initiating ART with decreasing CD4+ cell count compared with those with higher CD4+ cell count who do not yet need treatment. Women who initiated ART before the universal ART guidelines were issued were more likely to have advanced HIV disease, lower nadir CD4+ cell counts, and higher HIV viral loads than those who had not yet started ART.]

Access to effective cervical cancer screening, timely treatment of precancerous lesions, and timely access to ART all have an impact on ICC

Fig. 5.1 Proportion of the global population aged 15–49 years living with HIV, 2019
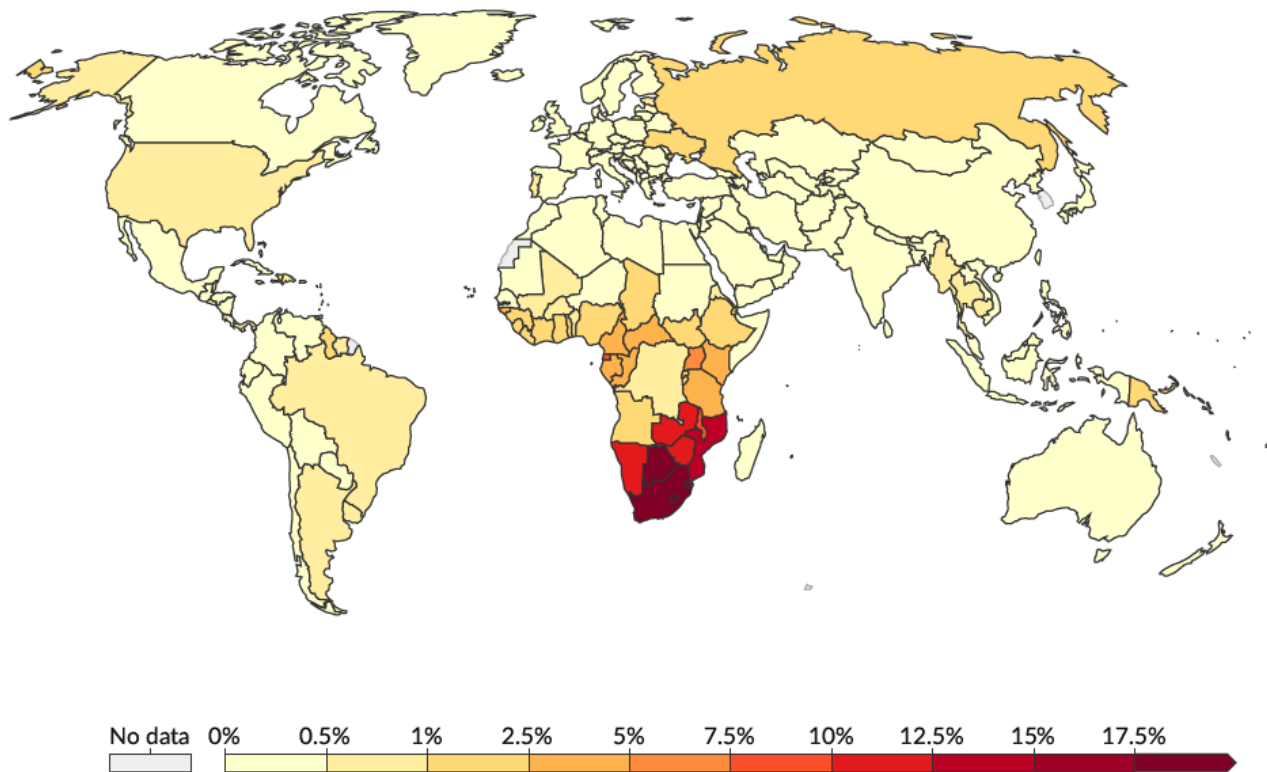
From Roser & Ritchie (2019).

incidence in WLHIV. In a study in WLHIV who initiated ART in 1996–2014 across four continents, ICC incidence rates were high in WLHIV in all regions but were observed to be 11-fold higher in South Africa (adjusted HR, 10.66; 95% CI, 6.73–16.88) and 2-fold higher in Latin America (adjusted HR, 2.43; 95% CI, 1.27–4.68) compared with the ratios observed in WLHIV in Europe or North America (Rohner et al., 2020). WLHIV who initiate ART at a higher CD4+ cell count and are adherent to treatment have more complete immune restoration, better virological control, a lower risk of HPV acquisition, and a higher likelihood of regression of cervical lesions (Palefsky, 2017). In a 21-year multisite prospective cohort study in the USA that enrolled 1807 WLHIV and 488 HIV-negative women in a

prevention programme (20 561 person-years of observation), the estimated incidence of ICC did not differ significantly by HIV status (HIV-negative: 0 per 100 000 person-years vs HIV-positive: 19.5 per 100 000 person-years; P = 0.53) (Massad et al., 2017). [The findings from these studies might be different in WLHIV in low- and middle-income countries (LMICs), who may not have early access to effective ART and frequent cervical cancer screening.]

(b) *Cervical cancer screening options for WLHIV*

There is growing evidence from countries with a high burden of HIV infection that cervical cancer screening is associated with a reduction in the incidence of ICC. A study in 10 640 WLHIV

in South Africa in 2004–2011 reported that ICC incidence decreased in WLHIV initiating ART from 2009 onwards, when the cytology-based cervical cancer screening programme and access to treatment of cervical lesions were expanded (260 vs 615 per 100 000 person-years for post-2009 vs pre-2005; adjusted HR, 0.42; 95% CI, 0.20–0.87) (Rohner et al., 2017).

Considering the differences in the natural history of HPV infection in WLHIV compared with women in the general population, WHO has developed cervical cancer screening guidelines adapted for WLHIV (WHO, 2021). In developing these guidelines, WHO considered the cost, availability, and performance of the screening tests and ready access to treatment facilities allowing rapid scale-up in LMICs. In an effort to increase the coverage of cervical cancer screening for WLHIV, several countries have adopted an approach that integrates HIV health care with cervical cancer screening services. Integration of cervical cancer screening services within HIV treatment services ensures that women at high risk of developing cervical cancer precursor lesions are screened; it also leads to continuity in primary prevention, favouring the early detection and management of HPV-associated cervical lesions, with minimal loss to follow-up (Sigfrid et al., 2017). The long-term effectiveness of such integration programmes on cervical cancer and HIV care is still unknown.

Initiatives to support cervical cancer screening in HIV care have been shown to increase screening participation in WLHIV. In a cross-sectional survey of WLHIV attending HIV clinics in Côte d'Ivoire, 1444 of 1991 women (72.5%) had been offered cervical cancer screening, mainly in the HIV clinic (88.9%). Factors associated with participation in cervical cancer screening included being informed about cervical cancer at the HIV clinic (adjusted OR, 1.5; 95% CI, 1.1–2.0), identifying HIV infection as a risk factor for cervical cancer (adjusted OR, 1.4; 95% CI, 1.1–1.8), being offered cervical cancer screening in the HIV clinic (adjusted OR, 10.1; 95% CI, 7.6–13.5), and university education level (adjusted OR, 2.1; 95% CI, 1.4–3.1) (Tchounga et al., 2019). [For this approach to achieve the desired effect of cervical cancer prevention in WLHIV, adequate treatment facilities offering ablative (cryotherapy, thermal ablation) and excisional (large loop electrosurgical excision procedure [LEEP]) treatment methods need to be readily available within screening facilities, and referral structures need to be established.]

(i) Cytology

The performance of cytology in cervical cancer screening in WLHIV has been shown to be similar to that in women in the general population. Conventional cervical cytology using the Papanicolaou method has variable sensitivity and specificity for both CIN2+ and CIN3+ in WLHIV. The sensitivity of cytology at a threshold of atypical squamous cells of undetermined significance or worse (ASC-US+) for detection of CIN2+ ranges from 52.5% to 100.0%, and the specificity from 13.2% to 94.5% (Maiman et al., 1998; Branca et al., 2001; Cohn et al., 2001; Anderson et al., 2006; Kitchener et al., 2007; Sahasrabuddhe et al., 2012; Mabeya et al., 2012; Chung et al., 2013; Firnhaber et al., 2013; Joshi et al., 2013; Bateman et al., 2014; Ndizeye et al., 2019). A large variability has also been observed for low-grade squamous intraepithelial lesion or worse (LSIL+): the sensitivity ranges from 52.0% to 97.4% and the specificity from 35.1% to 96.0%; and for HSIL+: the sensitivity ranges from 20.0% to 78.4% and the specificity from 58.3% to 99.2%. In countries with well-established cytology-based screening programmes, cytology has good accuracy for detection of CIN2+. High sensitivity and specificity for CIN2+ using HSIL+ cytology were reported in 1193 WLHIV in South Africa (sensitivity, 75.8%; 95% CI, 70.8–80.8%; specificity, 83.4%; 95% CI, 80.9–85.9%) (Firnhaber et al., 2013) and in 498 WLHIV in Kenya (sensitivity,

71.8%; 95% CI, 62.8–79.4%; specificity, 97.1%; 95% CI, 94.7–98.4%) (Chung et al., 2013).

The long-term impact of a cytology-based screening programme in WLHIV was evaluated in the Women's Interagency HIV Study (WIHS) in the USA, in which WLHIV were followed up for a median of 11 years with 6-monthly cytology and early referral for treatment of HSIL+. Four cases of ICC were observed in 1807 WLHIV during 20 561 person-years of observation, corresponding to an incidence rate of 19.5 cases per 100 000 person-years. No ICC cases were observed in HIV-negative women identified from regional cancer registries ($P = 0.53$) (Massad et al., 2017).

Few studies have evaluated the association between HIV-related factors and the diagnostic accuracy of cervical cytology. A study in 498 WLHIV in Kenya reported no association between CD4+ T-cell count or ART status and the diagnostic accuracy of cytology for CIN2+, irrespective of the cytology threshold used (Chung et al., 2013). In studies that provided a direct comparison of test strategies in WLHIV, HSIL+ cytology had a similar sensitivity for CIN2+ but a higher specificity compared with HPV DNA testing, whereas HSIL+ cytology had a lower sensitivity but a higher specificity (Kitchener et al., 2007; Chung et al., 2013; Firnhaber et al., 2013; Ndizeye et al., 2019).

(ii)   Visual inspection methods

The performance of VIA or visual inspection with Lugol's iodine (VILI) in screening WLHIV has been in evaluated in several studies. Ten studies (eight in sub-Saharan Africa and two in India) evaluated VIA for the detection of histologically verified CIN2+ in WLHIV; the sensitivity of VIA ranged from 48.4% to 86.6% and the specificity ranged from 47.3% to 96.7% (Kuhn et al., 2010; Mabeya et al., 2012; Sahasrabuddhe et al., 2012; Chung et al., 2013; Firnhaber et al., 2013; Joshi et al., 2013; Huchko et al., 2014; Bansil et al., 2015; Chibwesha et al.,

2016; Ndizeye et al., 2019). The sensitivity of VIA for the detection of CIN3+ was similarly heterogeneous (range, 53.8–100.0%). The sensitivity was lower in studies with a high proportion (> 70%) of women with histological verification of CIN2+ or CIN3+ (Mabeya et al., 2012; Chung et al., 2013; Firnhaber et al., 2013; Bansil et al., 2015; Chibwesha et al., 2016). The sensitivity was highest in studies that had frequent training and supervision of VIA providers and for which quality assurance and quality control procedures, including review of digital cervicography, were undertaken (Firnhaber et al., 2013; Joshi et al., 2013; Bateman et al., 2014; Huchko et al., 2014; Chibwesha et al., 2016). In a study in 498 WLHIV attending routine HIV care in Kenya, the sensitivity of VIA was lower in WLHIV aged 40 years or older (47.3%) than in those younger than 40 years (78.2%) (Chung et al., 2013). In four studies, the sensitivity of VIA was lower in WLHIV with a CD4+ T-cell count > 350 cells/µL (range, 54.9–87.9%) than in those with a CD4+ T-cell count ≤ 350 cells/µL (range, 69.5–94.1%) but with correspondingly higher specificity (Sahasrabuddhe et al., 2012; Chung et al., 2013; Firnhaber et al., 2013; Huchko et al., 2014). The higher sensitivity of VIA in WLHIV with a lower CD4+ T-cell count could be attributed to the larger, well-demarcated, and more easily identifiable acetowhite lesions observed in those women (Sahasrabuddhe et al., 2012).

Two studies evaluated the diagnostic accuracy of VIA for CIN2+ according to HIV status, with contrasting findings. In 1756 HIV-negative women and 386 WLHIV in a population-based cervical cancer screening study in Uganda, the sensitivity and specificity of VIA for CIN2+ were lower in WLHIV than in HIV-negative women (sensitivity, 77.1% vs 93.8%; specificity, 47.3% vs 60.5%) (Bansil et al., 2015). In a randomized clinical trial of two screen-and-treat strategies in 6555 women in South Africa, 956 of whom were HIV-positive, the sensitivity of VIA for the cumulative detection of CIN2+ over 36 months

was higher in WLHIV than in HIV-negative women (63.9% vs 47.8%), but the specificity was marginally lower (73.6% vs 80.3%) ([Kuhn et al., 2010](#)).

In a two-arm randomized study comparing VIA and VILI in detecting cytology-diagnosed SIL in Nigeria, VILI was found to be less sensitive and less specific in WLHIV, especially those with severe immunosuppression ([Ezechi et al., 2016](#)). In an RCT in 654 WLHIV randomized to undergo either VIA or VILI in Kenya, the performances of VIA and VILI were found to be similar; the sensitivity was 84.0% for VIA and 84.2% for VILI, and the specificity was 78.6% for VIA and 76.4% for VILI ([Huchko et al., 2015](#)). The use of VILI as a sequential test in WLHIV with a positive VIA test result did not increase the detection rate or the PPV for histologically verified CIN2+.

(iii)   HPV testing

Several studies have evaluated HPV DNA testing in WLHIV, mostly in sub-Saharan Africa ([Table 5.2](#)); they have reported consistently high sensitivity but variable specificity of HPV DNA tests for histologically verified CIN2+. Sensitivity estimates for CIN2+ were 88.8–94.6% (Hybrid Capture 2 [HC2]) ([Womack et al., 2000](#); [Cohn et al., 2001](#); [Kitchener et al., 2007](#); [Kuhn et al., 2010](#); [Firnhaber et al., 2013](#); [Joshi et al., 2013](#); [Ngou et al., 2013](#)), 88.0–93.6% (GeneXpert) ([Chibwesha et al., 2016](#); [Mbulawa et al., 2016](#); [Kuhn et al., 2020](#)); 92.2–100.0% (*care*HPV) ([Bansil et al., 2015](#); [Segondy et al., 2016](#)), and 78.0–83.6% (GP5+/6+ polymerase chain reaction [PCR] enzyme immunoassay [EIA]) ([Chung et al., 2013](#); [Kremer et al., 2019](#)), and the specificity was 41.3–77.4% (HC2), 48.3–60.0% (GeneXpert), 54.7–62.4% (*care*HPV), and 55.7–72.2% (GP5+/6+ PCR EIA).

A meta-regression of 20 studies on the relationship between the prevalence of carcinogenic HPV infection and the specificity of HPV DNA testing (HC2) for the presence of CIN2+ reported that for a 10% increase in the prevalence of carcinogenic HPV infection, the specificity of HC2 decreased by 8.4% (95% CI, 8.02–8.81%), and that the variation in the prevalence of carcinogenic HPV types explained 98% of the variability in the specificity of HC2 ([Giorgi-Rossi et al., 2012](#)). In WLHIV, the high prevalence of HPV infection and co-infection with multiple carcinogenic HPV types, many of which may be transient infections, results in low specificity of HPV DNA tests for CIN2+.

The prevalence of carcinogenic HPV types has been shown to be lower in women who are controlling HIV, i.e. those with prolonged ART use, sustained HIV viral suppression, and stable high CD4+ cell counts ([Kelly et al., 2018](#)). Therefore, HPV DNA tests have higher specificity to distinguish CIN2+ in women with a higher CD4+ cell count and/or prolonged ART use. In three studies that evaluated the diagnostic accuracy of HPV DNA tests (two using HC2 and one using GP5+/6+ PCR EIA) by CD4+ cell count, the specificity ranged from 31.6% to 45.7% in WLHIV with a CD4+ cell count ≤ 350 cells/μL and from 59.7% to 63.5% in WLHIV with a CD4+ cell count > 350 cells/μL, with some loss in sensitivity ([Chung et al., 2013](#); [Firnhaber et al., 2013](#); [Segondy et al., 2016](#)).

Because of the high prevalence of infection with multiple carcinogenic HPV types and the broad range of carcinogenic HPV types in WLHIV ([Clifford et al., 2006](#)), which may be a combination of incident and persistent infections, an approach using restricted genotyping may increase specificity for CIN2+. A cross-sectional study in 535 WLHIV in South Africa reported specificity to distinguish CIN2+ of 59.9% (95% CI, 54.1–65.7%) when using the GeneXpert five-channel approach (positive for any of 14 high-risk HPV [hrHPV] types: HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and/or 68) and specificity of 67.5% (95% CI, 62.0–73.1%) when using a restricted GeneXpert three-channel approach (positive for any of 8 hrHPV types: HPV types

Table 5.2 Sensitivity and specificity of HPV DNA testing for the detection of histologically verified CIN2+ in women living with HIV

Reference	Country	No. of WLHIV	Test evaluated	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Womack et al. (2000)	Zimbabwe	249	Hybrid Capture 2	90.7 (77.9–97.4)	41.3 (34.5–48.3)
Cohn et al. (2001)	USA	109	Hybrid Capture 2	90 (60–100)	48 (38–59)
Kitchener et al. (2007)	England, France, Ireland, Italy, Poland, Scotland, South Africa	1534	Hybrid Capture 2	91.3 (82.9–99.1)	47.7 (44.2–51.4)
Kuhn et al. (2010)	South Africa	956	Hybrid Capture 2	94.4 (81.3–99.3)	64.4 (58.0–70.3)
Chung et al. (2013)	Kenya	500	GP5+/6+	83.6 (75.6–89.4)	55.7 (50.4–60.9)
Firnhaber et al. (2013)	South Africa	1202	Hybrid Capture 2	91.9 (88.5–95.3)	51.4 (48.0–54.8)
Joshi et al. (2013)	India	1128	Hybrid Capture 2	94.6 (84.9–98.9)	77.4 (74.8–79.9)
Bansil et al. (2015)	Uganda	272	*care*HPV	94.3 (80.8–99.3)	62.4 (55.9–68.6)
Ngou et al. (2015)	Burkina Faso, South Africa	1224	Hybrid Capture 2	88.8 (82.9–93.2)	55.2 (52.1–58.4)
Chibwesha et al. (2016)	Zambia	200	GeneXpert	88 (71–97)	60 (52–68)
Mbulawa et al. (2016)	South Africa	1161	GeneXpert	88.3 (83.6–93.0)	48.4 (44.9–51.9)
Segondy et al. (2016)	Burkina Faso	444	*care*HPV	100.0 (66.4–100.0)	54.7 (49.9–59.5)
Segondy et al. (2016)	South Africa	499	*care*HPV	92.2 (81.1–97.8)	60.9 (56.3–65.5)
Kremer et al. (2019)	South Africa	285	GP5+/6+	78.0 (69.5–86.5)	72.2 (65.9–78.5)
Ndizeye et al. (2019)	Burundi	680	Riatol quantitative PCR	100.0 (100.0–100.0)	63.6 (59.9–67.3)
Kuhn et al. (2020)	South Africa	535	GeneXpert	93.6 (90.0–97.3)	59.9 (54.1–65.7)

CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus; PCR, polymerase chain reaction; WLHIV, women living with HIV.
Compiled with data from Viviano et al. (2017).

16, 18, 31, 33, 35, 45, 52, and/or 58), with minimal loss in sensitivity (93.6% and 90.7%, respectively) (Kuhn et al., 2020). The corresponding screen positivity for the five-channel approach and the three-channel approach was 48.8% and 41.5%, respectively, and the PPV was 31.7% and 35.0%, respectively. In the same study, a user-applied modification to increase the threshold to define screen-positive results using the three-channel approach further increased specificity to 77.0%, with some loss in sensitivity (85.0%). The corresponding estimates for screen positivity and PPV were 33.5% and 43.1%, respectively. [Such user-applied modifications for genotype restriction and screen-positivity threshold enable implementers to balance the capacity to refer hrHPV-positive women for colposcopy or treatment. In settings where colposcopy resources are limited or overtreatment is less tolerated, a high PPV is preferable, and in settings where women may be screened less frequently and/or few alternative treatment options are available, higher sensitivity may be preferred at a cost of a lower PPV.]

Few prospective studies have evaluated the effectiveness of HPV DNA screening in WLHIV. In an RCT of two screen-and-treat strategies in 956 WLHIV enrolled in South Africa in 2002–2002, before widespread availability of

ART, women were randomized to screen-and-treat with either HPV DNA testing or VIA or to a control group (evaluation or treatment was delayed for 6 months) and followed up for 36 months. In the screen-and-treat group with HPV DNA testing, there was an 80% reduction in CIN2+ over 36 months (RR, 0.20; 95% CI, 0.06–0.69), but in the screen-and-treat group with VIA, the reduction was 49% (RR, 0.51; 95% CI, 0.29–0.89) [possibly resulting from the low sensitivity of VIA at enrolment to detect CIN2+ over 36 months (63.9%; 95% CI, 46.2–79.2%) compared with that of HPV DNA testing (94.4%; 95% CI, 81.3–99.3%) and its lower negative predictive value (NPV) (VIA, 90.9%; 95% CI, 85.8–96.0%; HPV DNA, 97.2%; 95% CI, 87.0–99.4%)] (Kuhn et al., 2010).

As the technology of HPV testing becomes cheaper and less cumbersome to use, with the development of near-to-patient testing technologies, HPV testing is becoming easier to implement in LMICs where the burden of HIV infection remains very high. The available near-to-patient testing technologies for the detection of HPV require limited infrastructure, and with some tests the results can be available within 1 hour, potentially enabling same-day screen-and-treat approaches (Chibwesha et al., 2016). HPV testing can be effective in addressing many of the barriers to screening faced in low-resource settings. In a study in Uganda that compared the performance of HPV testing and VIA, the sensitivity of HPV testing in detecting HSIL+ was higher in WLHIV than in HIV-negative women (Bansil et al., 2015). In the HPV in Africa Research Partnership (HARP) study, conducted in Burkina Faso and South Africa, in 1052 WLHIV, the sensitivity of careHPV in detecting HSIL+ was 93.3% (95% CI, 83.8–98.2%) and the specificity was 57.9% (95% CI, 54.5–61.2%), and the specificity was observed to increase with the CD4+ cell count (Segondy et al., 2016).

In an effort to increase the coverage of cervical cancer screening in WLHIV, testing for HPV in self-collected cervicovaginal samples has been evaluated and found to be accurate and acceptable; the agreement between self-collected and clinician-collected samples ranged from 92% to 94% (kappa range, 0.71–0.88) (Petignat et al., 2005; Safaeian et al., 2007; Adamson et al., 2015; Obiri-Yeboah et al., 2017; Elliott et al., 2019; Thay et al., 2019), and agreement did not differ by HIV status (Safaeian et al., 2007; Obiri-Yeboah et al., 2017). A study in WLHIV and HIV-negative women in Zimbabwe also found that self-sampling was well accepted in both groups (Dube Mandishora et al., 2017).

(c) Triage options for WLHIV after a positive hrHPV test result

Given the high prevalence of carcinogenic HPV types and the low specificity of HPV DNA tests to distinguish CIN2+ in WLHIV, studies have evaluated various triage options in WLHIV after a positive hrHPV test result. A study in 300 WLHIV in Botswana evaluated different triage methods in hrHPV-positive (using GeneXpert) WLHIV, 33.0% of whom had histologically verified CIN2+. The study reported a sensitivity for CIN2+ of 83% with colposcopy, 59% with VIA, and 62% with cytology at a threshold of ASC-US+, a specificity of 49% with colposcopy, 49% with VIA, and 77% with cytology at a threshold of ASC-US+, and a PPV of 47% with colposcopy, 39% with VIA, and 60% with cytology at a threshold of ASC-US+ (Luckett et al., 2019). A study in 251 hrHPV-positive (using GP5+/6+ PCR EIA) WLHIV in Kenya, 37.5% of whom had CIN2+, reported a sensitivity of 70%, a specificity of 63%, and a PPV of 54% for CIN2+ with VIA, and a sensitivity of 95%, a specificity of 46%, and a PPV of 51% for CIN2+ with cytology at a threshold of ASC-US+. The use of HSIL+ cytology decreased sensitivity (75%) but with an increase in specificity (97%) and PPV (93%) (Chung et al., 2013). A study in 256 hrHPV-positive (using Riatol PCR) WLHIV in Burundi, 7.4% of whom had CIN2+, reported a sensitivity of 84.2%, a specificity of

94.5%, and a PPV of 55.2% for CIN2+ with VIA (Ndizeye et al., 2019).

When screening for cervical cancer with HPV testing in WLHIV, adequate consideration should be given to sequential testing (WHO, 2021).

(d) Age to start screening for cervical cancer in WLHIV

There is no good-quality evidence on when cervical cancer screening should be started in WLHIV. On the basis of studies on the epidemiology and natural history of HPV infection in WLHIV, the updated WHO guidelines recommend that cervical cancer screening should be started in sexually active women and girls as soon as HIV infection is confirmed (WHO, 2021).

(e) Frequency of screening for cervical cancer in WLHIV

In WLHIV, the prevalence of HPV infection remains high across different age groups, unlike the progressive decrease with age observed in HIV-negative women (Mbulawa et al., 2015). WLHIV have a higher risk of incident and persistent infections with multiple carcinogenic HPV types, with the potential to develop ICC at a younger age compared with HIV-negative women (Moscicki et al., 2004; Phanuphak et al., 2020). On the basis of studies on the natural history of HPV infection in WLHIV, most guidelines have recommended screening intervals as short as 12 months, taking prior screening test results into consideration (WHO, 2021).

5.2.2 Screening of older women

After menopause, the marked reduction in estrogen levels results in atrophy of the female genital tract, which is associated with cervical stenosis and thinning of the epithelium; this results in potential difficulty in cervical cancer screening and interpretation of results. In postmenopausal women, speculum examination and the collection of cervical cancer screening specimens can sometimes cause significant discomfort and contact bleeding. Also, the cervix becomes more difficult to expose and the transformation zone gets smaller, moves into the endocervical canal, and becomes less accessible for correct specimen sampling, which may lead to cytological reports of unsatisfactory sample. These physiological changes result in challenges in screening older women, who often also experience changes with age that may make screening more prone to discomfort, may lower the accuracy of the result, and may result in potential harm from overtreatment. Therefore, it is imperative to determine the balance of benefits and harms of cervical cancer screening in older women and to define the age at which women with average or above-average risk should stop screening. In older women who still need to undergo cervical cancer screening, there is also the need to determine the best screening modality and the frequency of screening appropriate for this age group.

(a) Current recommendations

In well-screened populations, most guidelines recommend stopping screening at age 65 years in women with prior adequate negative screening history (Table 5.3). However, empirical evidence is scant on when to stop screening in inadequately screened or previously unscreened women, in women aged 65 years or older with previous treatment for HSIL+, and in women with continuing risk factors for the development of cervical cancer, such as immunosuppression (e.g. WLHIV). Although the evidence is limited, recently published guidelines for cervical cancer screening from the American Cancer Society (ACS) (Fontham et al., 2020) and for management of abnormal cervical cancer screening tests from the American Society for Colposcopy and Cervical Pathology (ASCCP) (Perkins et al., 2020) have addressed the issue of when to stop screening in these subpopulations of women.

(b) Cessation of screening

In general, a woman's previous screening history, continuing risk factors for the development of cervical cancer, and her wishes should be considered to determine the age at which to stop screening.

(i) Cessation of screening based on age and prior adequate screening history

The 2020 ACS and ASCCP guidelines in the USA recommend against cervical cancer screening in women older than 65 years who have prior adequate negative screening history and no history of CIN2 or a more severe diagnosis within the past 25 years (Fontham et al., 2020; Perkins et al., 2020). Adequate negative screening was defined as three negative results from cytology alone, two negative co-test results, or two negative primary HPV test results within the past 10 years, with the most recent test having occurred within the recommended interval of the test used (Fontham et al., 2020). For women with a history of treated lesions with high-grade histology or cytology who reach age 65 years and have completed the 25-year surveillance period (or when this period is completed after age 65 years), continuing surveillance at 3-year intervals is acceptable, provided the women are in reasonably good health (Perkins et al., 2020). In many other high-income countries, in women with prior adequate negative screening history, cessation of cervical cancer screening occurs at ages varying between 60 years and 69 years, although some countries, such as Japan and the Republic of Korea, screen women after age 70 years (Dowling et al., 2010; Castañón et al., 2014).

Because empirical data are lacking, these recommendations are based on the interpretation of the natural history of HPV infection, surveillance trends, expert opinion, and modelling. Although incident HPV infections in women aged 65 years or older are observed to be rare and are thought to have insufficient time to progress to ICC in the woman's lifetime, emerging data from co-testing and primary HPV screening call for caution in this interpretation (Gravitt et al., 2018).

(ii) Cessation of screening in women aged 65 years or older who have had no screening or an irregular screening history

In most LMICs, it is not unusual to find women aged 65 years or older who have never undergone screening for cervical cancer. In these women, the risk of cervical cancer is relatively high (Díaz del Arco et al., 2019). Even in high-income countries with well-established cervical cancer screening programmes, the proportion of women who attend screening decreases with increasing age (Pankakoski et al., 2020). Women with an inadequate screening history will probably benefit from continued screening beyond age 65 years, but limited clear empirical data are available to guide on when the screening should eventually stop. The current ACS guidelines specify that women with an inadequate screening history in the 10-year period before age 65 years should continue screening until a 10-year history of adequate negative screening is achieved, and for women with a prior diagnosis of CIN2+, the ASCCP and ACS guidelines recommend that screening should continue until a 25-year history of adequate negative screening is achieved, even if screening is extended beyond age 65 years (Fontham et al., 2020; Perkins et al., 2020). The guidelines of both organizations state that women can stop screening once these milestones are achieved.

(iii) Cessation of screening in women aged 65 years or older with previous treatment for HSIL+ and those with continuing risk factors such as immunosuppression

Women treated for histologically confirmed HSIL+ have a higher risk of recurrence and development of ICC (Soutter et al., 2006). The ACS and ASCCP guidelines recommend that cervical

Table 5.3 National guidelines on when to stop screening for cervical cancer

Country	Screening test (frequency of screening)	Age to stop screening (years)	Authority (reference)
Australia	Cytology (every 5 yr) Primary HPV (every 5 yr)	74 74	Australian National Cervical Screening Program, 2017 (AIHW, 2019)
Brazil	Primary HPV (every 5 yr)	64	Brazil, 2016 (Zeferino et al., 2018)
China	Cytology (every 2 yr) HPV (every 5 yr)	65 65	China, 2017 (Aoki et al., 2020)
India	Cytology (every 5 yr) HPV (every 5 yr) VIA (every 5 yr)	65 65 50[a]	Federation of Obstetrics and Gynaecologic Societies of India (FOGSI), 2019 (Bhatla et al., 2020)
Indonesia	VIA (every 3–5 yr) Cytology (every 3–5 yr)	50 50	Indonesia, 2017 (Aoki et al., 2020)
Japan	Cytology (every 2 yr) HPV (every 2 yr)	75 75	Japan (Aoki et al., 2020)
Netherlands	Primary HPV (every 5 yr)	60	Netherlands, 2020 (RIVM, 2020)
South Africa	Cytology (every 10 yr)	50	Cervical Cancer Prevention and Control Policy, 2017 (National Department of Health South Africa, 2020)
Sweden	Cytology (every 3 yr) Cytology (every 5 yr) Primary HPV (every 5 yr)	49 60 60	Swedish national cervical screening programme, 2015 (NordScreen, 2017)
Thailand	VIA (every 5 yr) Cytology (every 5 yr) HPV primary screening (every 5 yr)	60 60 60	Thailand, 2020 (Aoki et al., 2020)
United Kingdom	Cytology (every 3 yr) HPV (every 5 yr)	65	United Kingdom National Screening Committee, 2016 (Public Health England, 2020)
USA	Cytology (every 3 yr) Primary HPV (every 5 yr) HPV with cytology co-testing (every 5 yr)	65[b]	American Cancer Society, 2020 (Fontham et al., 2020) United States Preventive Services Task Force Recommendations, 2018 (Curry et al., 2018)

CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papillomavirus; VIA, visual inspection with acetic acid; yr, year or years.

[a] Preferable.

[b] Adequate screening: a woman aged > 65 yr with no history of CIN2+ within the past 25 yr.

cancer screening should continue for 25 years from the time of treatment, even if screening is extended beyond age 65 years (Fontham et al., 2020; Perkins et al., 2020). Women with immunosuppression need to continue with cervical cancer screening for life (Perkins et al., 2020).

(c) Benefits of stopping screening at age 65 years

Although the benefit of the last negative cytology result decreases over time, the absolute risk of developing cervical cancer still remains very low in adequately screened older women.

In a case–control study in the United Kingdom, women with an adequate negative screening history at age 65 years had the lowest risk of cervical cancer compared with those not screened at age 50–64 years (20-year risk: 8 cancers per 10 000 women vs 49 cancers per 10 000 women) (Castañón et al., 2014; Malagón et al., 2018; Landy et al., 2020). The risk of a false-positive screening test result also increases significantly in women older than 50 years (Armaroli et al., 2008). Therefore, extending screening beyond age 65 years in adequately screened women is associated with potential harms of treating women

with false-positive results. [Unfortunately, the data on potential harms come mostly from modelling and not from empirical evidence.] Some authors have suggested that it may be necessary to re-evaluate model assumptions, because the published literature suggests that factors such as the high occurrence of hysterectomies, HPV latency and possible reactivation of infection, possible changes in sexual habits, and the age-specific differences in the sensitivity and specificity of screening strategies in older women may influence potential harms of screening in older women (Grainge et al., 2005; Rositch et al., 2012, 2014; Ermel & Fife, 2016).

(d) Benefits of screening in women aged 65 years or older

Cytological abnormalities and ICC are not rare occurrences in women aged 65 years or older (Çakmak & Köseoğlu, 2014; Díaz del Arco et al., 2019). In a nationwide audit of the cervical cancer screening programme in Sweden, 390 (31.7%) of 1230 cases of cervical cancer reported to the Swedish Cancer Registry in 1999–2001 occurred in women aged 66 years or older, most of whom (91.8%; 358 of 390) had not undergone screening in the preceding screening interval (Andrae et al., 2008). In women who are diagnosed with ICC after age 65 years, the disease is usually advanced and the prognosis is poor (Darlin et al., 2014).

Limited data are also available from small non-randomized studies, which have shown a benefit of screening older women in reducing the risk of ICC. A case–control study in the USA showed that even in older women, the protective benefit of a negative cytology test result does not last a lifetime but is lost 5–7 years after the last screening test (Kamineni et al., 2013). A case–control study in the United Kingdom examined the risk of developing ICC in women aged 65–83 years who had adequate negative screening (i.e. whose last three test results were negative) between ages 50 years and 64 years and those who were not screened between those ages. The risk of developing ICC after age 65 years was 4.0 per 100 000 women in the group who had adequate negative screening compared with 24.5 per 100 000 women in the unscreened group, corresponding to an 84% reduction in risk (Castañón et al., 2014). The risk of developing ICC in women whose screening was stopped at age 55 years was observed to be almost double that in women whose screening was stopped at age 65 years (379 vs 208 ICC cases per 100 000 women at age 55–84 years).

A mortality audit of the cervical cancer screening programme in Finland assessed the impact of screening at age 65 years on mortality reduction. The relative risk of death from cervical cancer for women invited for cervical cancer screening at age 65 years compared with those not invited was 0.52 (95% CI, 0.29–0.94). The relative risk of death for women not attending screening versus those not invited was 1.28 (CI, 0.65–2.50), and the relative risk of death for women attending screening versus those not invited was 0.28 (CI, 0.13–0.59) (Pankakoski et al., 2019).

In another mortality audit study in Finland, screening between ages 55 years and 69 years was observed to be as effective as screening between ages 40 years and 54 years. Odds ratios of the association between cervical cancer death and screening participation were calculated, to approximate the risk of death from ICC with diagnosis in the interval between screening invitations, and corrected for self-selection. The odds ratios were 0.33 (95% CI, 0.20–0.56) for women screened at age 40–54 years and 0.29 (95% CI, 0.16–0.54) for women screened at age 55–69 years (Lönnberg et al., 2013). The values suggest a trend towards a higher reduction in risk in women screened at age 65–69 years compared with women screened at age 40–54 years.

Other case–control studies and audits of national cervical cancer screening programmes have also shown some degree of protective benefit of screening older women (Sasieni et al., 2003,

2009). Using colposcopy referral (i.e. the clinical burden of screening) as a proxy for harm, modelling was used to estimate the possible harm of extending screening to age 75 years with screening intervals of 5 years. Extending screening beyond age 65 years was found to be associated with very small gains in life expectancy, at the expense of a large number of colposcopies (Kulasingam et al., 2013) [increasing the risks of potential harm].

Using data from the cervical cancer screening programme in Canada in a Markov model, it was shown that women without HPV vaccination but with cytology screening every 3 years between ages 25 years and 69 years would have a lifetime risk of cervical cancer of 1 in 532, and that increasing the age at which women stopped cytology screening from 55 years to 75 years led to incremental decreases in cancer risk later in life. In a woman aged 70 years with unknown screening history, the average lifetime risk of ICC was 1 in 588 (< 1%; 95% percentile interval, 1 in 451 to 1 in 873). The lifetime risk at age 70 years was decreased 2.0-fold (to 1 in 1206) with negative cytology alone, 12.9-fold (to 1 in 6525) with a negative HPV test result alone, and 18.1-fold (to 1 in 9550) with a negative co-test result for cytology and HPV testing (Malagón et al., 2018).

5.2.3 Screening of women with a personal history of precancerous lesions

Women with abnormal screening or diagnostic test results, with lesions that are either histologically confirmed or visually judged to be HSIL/CIN2+ or adenocarcinoma in situ (AIS), usually undergo treatment for the precancerous lesions to prevent progression to ICC. Although most women who have undergone treatment for precancerous cervical lesions do not experience a recurrence of disease, women who have undergone treatment for known or suspected combined CIN2+/AIS or HSIL/AIS are at higher risk of CIN3+, and thus should undergo post-treatment management and surveillance for

test of cure (TOC) before returning to routine screening (Table 5.4). This section focuses on screening after treatment for biopsy-confirmed HSIL/CIN2+ or AIS.

During the past two decades, particularly because of the shift towards HPV-based cervical cancer screening, guidelines and national programmes have continued to evolve to manage abnormalities identified at screening that benefit from short-term surveillance rather than referral for colposcopy, or from surveillance after colposcopy rather than proceeding directly to treatment. These surveillance algorithms before or after colposcopy are intended to avoid overtreatment, especially in women of reproductive age. However, for women who are treated for known or suspected precancerous lesions, national and international guidelines specify post-treatment follow-up protocols for TOC before recommending the return to routine screening. Over time, and with longer post-treatment follow-up studies (Soutter et al., 1997), there has been greater recognition of continuing risk and, more recently, the degree to which test results before and after treatment are predictive of risk (Katki et al., 2013). In higher-resource settings, recommendations have evolved with a greater understanding of the role of persistent infection with carcinogenic HPV types and the critical role of HPV testing in defining risk and follow-up algorithms. Given the complexity of an overwhelming number of potential combinations of testing and triage, some guidelines are replacing results-based protocols with simpler, risk-based protocols based on prior screening test results, current test results, and a woman's age, following the principle of equal management for equal risk; these extend to post-treatment surveillance and return-to-screening protocols (WHO, 2014; Cheung et al., 2020; Demarco et al., 2020; Egemen et al., 2020; Perkins et al., 2020; Schiffman et al., 2020).

Table 5.4 Screening after treatment for precancerous lesions, by pre-treatment diagnosis and country or authority

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
Squamous intraepithelial lesions				
Australia Cancer Council Australia ([Cancer Council Australia Cervical Cancer Screening Guidelines Working Party, 2020](#))	HSIL/CIN2/3	HPV-based test with LBC at 12 mo. Annual testing after the first follow-up test until 2 negative co-tests	Return to routine screening every 5 yr	Any positive carcinogenic HPV (HPV16/18) test result should lead to referral for colposcopy, regardless of the cytology result. Consult recommendations for positive non-HPV16/18 test findings, glandular abnormality, or abnormal LBC findings with negative HPV test findings
Brazil Brazilian Association for the Lower Genital Tract Pathology and Colposcopy (ABPTGIC) ([Zeferino et al., 2018](#))	CIN2/3	HPV DNA test between 6 mo and 12 mo after treatment (A)	If cleared of oncogenic types, return to cytology screening every 3 yr (A)	None
Canada Multi-organization guideline ([Bentley et al., 2012](#))	CIN2+	Colposcopy and cytology every 6 mo for 1–2 yr	If follow-up tests are normal, return to annual cytology	None
France National Cancer Institute: Post-treatment surveillance of precancerous lesions of the uterine cervix ([INCa, 2019](#))	HSIL	Regardless of margin status, hrHPV test at 6 mo (B). If negative, repeat HPV test after 3 yr, then again after 3 yr (B), then prolonged surveillance (B) (test and testing interval not specified) without age limit (C); if positive, colposcopy with examination of vulva and vagina and biopsy if deemed necessary (B). If colposcopy satisfactory and no lesion identified, HPV test at 12 mo (B)	If hrHPV-negative at 6 mo after treatment, followed by 2 negative HPV tests every 3 yr, continue prolonged surveillance (B), without age limit (C)	Data from the literature did not enable the precise modalities or periodicity of this surveillance to be determined
New Zealand ([Ministry of Health New Zealand, 2020](#))	HSIL/CIN2/3	Co-testing (cytology and hrHPV test) at 6 mo; repeat after 12 mo for TOC	Cytology every 3 yr	Where there are clinical concerns, perform colposcopy with co-testing at 6 mo after treatment. If HPV test is positive at 6 mo or 18 mo after treatment, return to colposcopy. If colposcopy is negative, continue annual co-testing until 2 consecutive negative co-tests 1 yr apart

Table 5.4 (continued)

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
South Africa (National Department of Health South Africa, 2020)	CIN2/3	Cytology (conventional or LBC) after 12 mo. After the follow-up visit at 12 mo, women should have another screening test 3 yr after treatment (NG)	When cytology has returned to normal, the recommended screening interval should be followed, i.e. every 3 yr for women at high risk (e.g. HIV-positive women, recipients of organ transplant, and women with immunosuppressive disease or undergoing immunosuppressant treatment) and every 10 yr for women at low risk (NG)	None
Spain Spanish Association of Cervical Pathology and Colposcopy (AEPCC, 2015)	HSIL/CIN2/3	If negative margins, co-test at 6 mo; if negative, co-test at 24 mo; if negative, co-test at 3 yr	HPV test every 5 yr for up to 20 yr regardless of age	None
United Kingdom (Public Health England, 2016)	Previous treatment for CIN	Cytology at 6 mo, with triage based on cytology findings	Cytology every 3 yr	At 6 mo, women with negative, borderline, or low-grade findings should undergo reflex hrHPV testing; women with negative test results should be returned to community-based routine recall for cytology in 3 yr

Table 5.4 (continued)

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
USA ASCCP ([Perkins et al., 2020](#))	HSIL/CIN2+	At 6 mo, regardless of margin status: HPV-based testing (preferred) (BII); after the initial test, HPV-based testing annually for 3 yr (preferred) (AII) Follow-up with colposcopy and ECC (acceptable)	Upon completion of short-term protocol, HPV-based testing every 3 yr for 25 yr, even if surveillance extends beyond age 65 yr (BII) If 25-yr surveillance has been completed, continued screening every 3 yr is acceptable as long as the patient is in good health (BIII). Patients with limited life expectancy can discontinue screening	If HPV-based tests are positive, colposcopy and biopsies should be performed (AII)
		At 6 mo, regardless of margin status, cytology alone. Followed by cytology every 6 mo for 3 yr (NG)	Upon completion of short-term protocol, cytology every year for 25 yr, even if surveillance extends beyond age 65 yr Implied: Transition to HPV testing at the earliest opportunity (NG)	Cytology alone is acceptable only if HPV-based testing is not feasible Cytology should only be used for patients younger than age 25 yr, with transition to HPV-based testing after age 25 yr
World Health Organization ([WHO, 2014](#))	HSIL/CIN2+	At 12 mo, primary HPV test, cytology, or VIA (NG) If CIN3 confirmed on histopathology at the time of treatment, rescreening is recommended annually for 3 yr. If these rescreens are negative, return to routine screening	If normal results at 12 mo, return to routine screening If annual rescreening for CIN3 detected at the time of treatment is negative, return to routine screening at programme intervals	If the follow-up test is positive, indicating persistence or recurrence of cervical precancer, retreatment is needed, following protocols based on biopsy results and second treatment considerations
Adenocarcinoma				
Brazil Brazilian Association for the Lower Genital Tract Pathology and Colposcopy (ABPTGIC) ([Zeferino et al., 2018](#))	AIS	HPV DNA test between 6 mo and 12 mo after treatment (A)	If cleared of oncogenic types, return to cytology screening every 3 yr (A)	None

Table 5.4 (continued)

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
Canada Multi-organization guideline (Bentley et al., 2012)	AIS	For women who wish to preserve fertility, colposcopy, ECC, and cytology every 6–12 mo for at least 5 yr If childbearing is complete, hysterectomy should be considered	Consider hrHPV testing Annual cytology testing	If negative margins cannot be achieved, hysterectomy should be considered
France National Cancer Institute: Post-treatment surveillance of precancerous lesions of the uterine cervix (INCa, 2019)	AIS	For women who wish to preserve fertility, if margins are disease-free, hrHPV test at 6 mo (C). If negative, annual follow-up; if positive, colposcopy with examination of vulva and vagina and biopsy if deemed necessary, ± ECC (C). If colposcopy satisfactory and no lesion identified, HPV test at 12 mo (C) If childbearing is complete, hysterectomy is recommended. Surveillance is similar to that of HSIL (C)	If HPV test at 6 mo is negative, do not return to routine screening; annual follow-up is recommended (C)	Data from the literature did not enable the modalities of this surveillance to be determined precisely; it will be based on existing tests (cytology, HPV test, colposcopy, and ECC). After childbearing is complete, hysterectomy should be discussed with the woman
New Zealand (Ministry of Health New Zealand, 2020)	AIS	Management will depend on age, fertility expectations, and clear excision margins. Follow-up colposcopy and cytology (including endocervical brush sample) at 6 mo after treatment. Repeat cytology at 12 mo	Annual cytology	The guideline cites a lack of randomized studies of people with AIS, but notes for people with fertility expectations who have clear margins, 2 consecutive negative annual HPV tests have a PPV for no identifiable disease of 100%
Spain Spanish Association of Cervical Pathology and Colposcopy (AEPCC, 2015)	AIS	If childbearing is complete, hysterectomy is recommended For women who wish to preserve fertility, if margins are disease-free, follow-up with colposcopy, endocervical sampling, and cytology every 6 mo for 24 mo, with HPV test at 24 mo	HPV test every 3 yr	None

Table 5.4   (continued)

Country Authority (reference)	Pre-treatment diagnosis	Short-term recommendation (and evidence grades[a])	Long-term recommendation (and evidence grades[a])	Considerations
USA ASCCP (Perkins et al., 2020) SGO (Teoh et al., 2020)	AIS, with fertility-sparing treatment	HPV-based testing with endocervical sampling every 6 mo for 3 yr	After 3 yr, annual HPV-based testing with or without endocervical sampling for a least 2 yr, or until hysterectomy is performed (NG) or Continue HPV-based screening every 3 yr until hysterectomy, or for at least 25 yr	After year 5, women who have consistent negative test results may extend the surveillance interval to 3 yr, and continued surveillance is acceptable after childbearing. Hysterectomy is preferred after childbearing if the patient has had positive HPV or cytology results during surveillance (NG)
ASCCP (Perkins et al., 2020) SGO (Teoh et al., 2020)	AIS, with hysterectomy	Vaginal HPV-based testing annually for 3 yr	Vaginal HPV-based testing every 3 yr for at least 25 yr	Follow ASCCP for 25 yr. Vaginal colposcopy is recommended for women with high-grade cytology results, persistent low-grade cytology results, or 2 or more positive HPV test results
World Health Organization (WHO, 2014)	AIS	At 12 mo, primary HPV test, cytology, or VIA (NG) If AIS confirmed on histopathology at the time of treatment, rescreening is recommended annually for 3 yr. If these rescreens are negative, return to routine screening	If normal results at 12 mo, return to routine screening If annual rescreening for AIS detected at the time of treatment is negative, return to routine screening at programme intervals	If the follow-up test is positive, indicating persistence or recurrence of cervical precancer, retreatment is needed, following protocols based on biopsy results and second treatment considerations
	Previous treatment for CIN	HPV-based testing at 6 mo If negative, repeat after 12 mo (18 mo after treatment)	If follow-up tests are normal, return to cytology every 3 yr	None

AIS, adenocarcinoma in situ; ASCCP, American Society for Colposcopy and Cervical Pathology; CIN, cervical intraepithelial neoplasia; CIN2+, CIN grade 2 or worse; ECC, endocervical curettage; HPV, human papillomavirus; hrHPV, high-risk HPV; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; mo, month or months; NG, not graded; PPV, positive predictive value; SGO, Society of Gynecologic Oncology; TOC, test of cure; VIA, visual inspection with acetic acid; yr, year or years.

[a] Each grade according to the specific grading of the respective authority.

A sample of current recommendations for follow-up of women treated for precancerous lesions is shown in Table 5.4, organized by the pre-treatment diagnosis, the date of issue, and the issuing authority, to highlight the variation in protocols and, to some extent, the evolution in recommendations over time with the accumulation of evidence on post-treatment risk and other considerations. The recommendations are heterogeneous for HSIL/CIN2+ or AIS; this probably reflects varying health resources, the available testing technology, the available evidence within the guideline development cycle, and whether follow-up protocols are based on an indication of risk associated with pre-treatment indications and absence of clear margins after treatment, or calculated estimates of absolute risk based on prior screening test and biopsy results, current surveillance test results, and individual factors such as age, pregnancy, and immunosuppression (WHO, 2014; von Karsa et al., 2015; Perkins et al., 2020). Recommendations that take into account fertility preservation, pregnancy, diagnosis of AIS, and high-risk immunosuppressed conditions (HIV infection, autoimmune conditions, persistent HPV infection, use of immunosuppressant therapy, etc.) show greater similarity (Chin-Hong, 2016; Davis et al., 2016; Carriero et al., 2018; Kim et al., 2018; Moscicki et al., 2019). In some instances, follow-up protocols for TOC are the same for HSIL/CIN2+ or AIS. [All recommendations shown in Table 5.4 are current, but updates may be in progress and/or prevalent protocols in a country may have evolved ahead of a guideline update in response to new evidence.]

(a)   Personal history of HSIL/CIN2+

(i)   Increase in risk

An increased risk of HSIL/CIN2+ and ICC has been observed in long-term follow-up studies of women treated for precancerous lesions. A study in the United Kingdom, commissioned by the National Health Service Cervical Cancer Screening Programme, sought to determine the duration of an elevated rate of ICC and vaginal cancer after treatment for CIN (Soutter et al., 2006). Analysis of 26 cohorts in 25 studies in Asia, Europe, and North America, in which follow-up ranged from 5 years to 25 years, showed an increased risk (~2.8 times the background risk) of post-treatment ICC for up to 20 years. The incidence rate of reported post-treatment CIN ranged from 76 to 6036 per 100 000 women-years (median, 1413 per 100 000 women-years) and was greatest in the first year after treatment; this was probably due to a combination of residual and recurrent disease. In contrast to the persistent elevated incidence of ICC, rates of post-treatment CIN fell steadily during the 10 years after treatment (Soutter et al., 2006).

Similar risks were observed in a retrospective cohort study in Finland, in which 7564 women were treated in 1974–2001 for CIN1–3 or CIN grade not otherwise specified. The average follow-up was 11.9 years (range, 0.5–28 years), and the standardized incidence ratio (SIR) for invasive disease was 2.8 (95% CI, 1.7–4.2) (Kalliala et al., 2005). In Sweden, 132 493 women were followed up after treatment for CIN3 in 1958–2002. Women with previous CIN3 had an increased risk of ICC compared with the general female population (SIR, 2.3; 95% CI, 2.2–2.5) (Strander et al., 2007). Both studies observed persistent elevated risk over more than 20 years. In the study in Finland, risk was highest in the second decade after treatment (Kalliala et al., 2005), whereas in the study in Sweden, risk decreased over time but remained elevated 25 years after treatment (Strander et al., 2007). In a study in Canada, the risk of CIN3+ within 1–5 years after treatment was evaluated in 14 668 women who had undergone treatment for CIN3 in 2006–2010, and a 5-year recurrence rate of CIN3 of 6.1% was observed, with increased risk independently associated with abnormal post-treatment cytology and age older than 45 years (Swift et al., 2020).

In an effort to update estimates of the risks of developing and dying from cervical cancer after treatment of precancerous lesions, Kalliala et al. (2020) conducted a pooled analysis of 27 studies of cervical cancer incidence after treatment of predominantly CIN3 (some studies included CIN1/2), with a mean or median follow-up of 5–27.5 years. [The analysis included some studies that were included in the pooled analysis by Soutter et al. (2006) as well as studies published since 2006, including several large national and regional population-based studies.] The investigators limited inclusion to studies with nationwide or regionwide cancer registries as a source of follow-up data, and presented data with at least 5 years of follow-up (Kalliala et al., 2020). A pooled absolute incidence rate of cervical cancer after treatment of CIN of 39 per 100 000 women-years was reported, with follow-up of more than 20 years after treatment (range, 31–38 per 100 000 women-years based on duration of follow-up). This is compared with the estimate from Soutter et al. (2006) of 56 per 100 000 women-years up to 20 years after treatment.

Incomplete excision of CIN also is associated with an increased risk of CIN of any grade or ICC. In a meta-analysis of 66 studies including 35 109 women who underwent treatment for CIN using excisional methods, 8091 (23%) of whom had at least one excisional margin with residual disease (incomplete excision), post-treatment high-grade disease (HSIL or CIN2/3) occurred in 18% of women who had incomplete excision compared with 3% of women who had complete excision (RR, 6.09; 95% CI, 3.87–9.60) (Ghaem-Maghami et al., 2007). A systematic review and meta-analysis was undertaken of 97 studies including 44 446 women treated for cervical precancer that evaluated the association between incomplete excision of precursor lesions and treatment failure, defined as the occurrence of residual or recurrent CIN2+. An increased risk of treatment failure was observed in women with positive resection margins compared with those with negative resection margins (17.1% vs 3.7%; RR, 4.8; 95% CI, 3.2–7.2) (Arbyn et al., 2017). However, additional analysis revealed that margin status was a lesser predictor of risk of residual or recurrent CIN2+ compared with hrHPV test results. The risk of post-treatment CIN2+ was 3.7% when margins were clear, whereas the risk of post-treatment CIN2+ associated with a concurrent negative hrHPV test result was 0.8% (Arbyn et al., 2017).

Five-year risks of CIN3+ after treatment for CIN2 or CIN3 (conservatively based on treatment for CIN3) were estimated on the basis of current HPV and cytology test results in women aged 25–65 years who underwent cervical cancer screening in the USA, to support the 2019 ASCCP Risk-Based Management Consensus Guidelines (Egemen et al., 2020). Women with a negative HPV test result after treatment had a 5-year risk of CIN3+ of 2.0%. A negative HPV test result combined with cytology negative for intraepithelial lesion or malignancy (NILM) was associated with a 5-year risk of CIN3+ of 1.7%, and a negative HPV test result combined with cytology negative for ASC-US/LSIL was associated with a 5-year risk of CIN3+ of 3.8%. In contrast, women with a negative HPV test result combined with high-grade cytology (atypical squamous cells, cannot exclude HSIL [ASC-H]/ atypical glandular cells [AGC]/HSIL+) had a 5-year risk of CIN3+ of 18% (Egemen et al., 2020). In a second study, also to support the ASCCP Risk-Based Management Consensus Guidelines, a systematic review was conducted of 23 studies in Asia, Europe, and North America published in 2012–2019 and including a broader spectrum of tests or diagnostic assays for post-colposcopy and post-treatment surveillance (Clarke et al., 2020). Follow-up periods, with interim examinations, ranged from 6 months to 121 months, although most were 24–36 months. In all studies combined, women who were HPV-negative after treatment had a risk of CIN2+ of 0.69% (95% CI, 0.3–1.5%), and women who were HPV-positive

after treatment had a risk of CIN2+ of 18.3% (95% CI, 12.1–26.6%). The risk of CIN2+ after treatment was higher in women with concurrent positive (ASC-US+) cytology (36.6%; 95% CI, 28.4–45.7%) than in women with concurrent negative cytology (1.7%; 95% CI, 1.0–3.1%) (Clarke et al., 2020).

(ii) Follow-up recommendations for return to screening

Recommendations for follow-up of women treated for HSIL/CIN2+ have evolved over time (Table 5.4). Most guidelines are based on currently available evidence, i.e. the follow-up interval (6 or 12 months) is determined by the pre-treatment diagnosis of SIL/CIN and the margin status after treatment. Although most recommendations shown in Table 5.4 specify initial *testing* protocols (cytology alone, co-testing, or primary HPV testing), surveillance intervals may be fixed (i.e. 6 months or 12 months after treatment) or they may be lengthened after successive normal test results while still accumulating a history of normal findings to support TOC. Surveillance periods range from a single test at 6 months after treatment to consecutive testing events over 3 years or more to establish TOC, after which women may be recommended to return to routine screening intervals. However, some recommendations also provide flexibility to allow for longer periods of surveillance on the basis of clinical concerns (Ministry of Health New Zealand, 2020). The WHO recommendations stress the importance of post-treatment surveillance for 3 years after a diagnosis of CIN3 but provide options for choice of test (HPV test, cytology, or VIA) to accommodate local capacity (WHO, 2014). Follow-up testing using HPV-based testing predominates after 2018, with variable criteria to determine TOC. For example, Cancer Council Australia recommends co-testing using liquid-based cytology (LBC) and HPV testing at 12 months and annually thereafter until there have been two consecutive negative co-test results before returning women to routine screening every 5 years (Cancer Council Australia Cervical Cancer Screening Guidelines Working Party, 2020). In contrast, in New Zealand, co-testing (cytology and HPV testing) is recommended at 6 months and again at 12 months to determine TOC, after which women may return to cytology-only testing every 3 years (Ministry of Health New Zealand, 2020).

In the USA, the ASCCP consensus guidelines are based on current screening test results and previous screening test and biopsy results (Perkins, et al., 2020). Risk-based post-treatment surveillance protocols recommend short-term HPV-based testing (6 months after treatment), followed by annual HPV-based tests for 3 years before returning women to a schedule approximating routine screening (HPV testing every 3 years [preferred] or annual cytology) (Perkins et al., 2020). When there are two or three negative follow-up HPV-based tests after treatment of CIN2/3, the 5-year risk of CIN3 is less than 1.0%, and it is considerably less with three negative test results than with two negative test results. When there are two consecutive negative follow-up co-test results after treatment, the 5-year risk of CIN3+ is 0.68%. One more negative co-test result decreases this risk to 0.35% (Egemen et al., 2020). Routine screening for women at average risk would be HPV-based testing every 5 years, but because the 5-year risk of CIN3 after three negative HPV-based test results is above the risk threshold (0.15%) set by ASCCP for 5-year HPV-based screening, and because this risk remains elevated for up to 25 years, screening every 3 years is recommended for a minimum of 25 years. As is the case with the ASCCP guidelines, some countries, such as South Africa, extend risk-stratified screening intervals into a long-term follow-up period (National Department of Health South Africa, 2020).

(b) Personal history of AIS

AIS is less common than HSIL/CIN2+, and there are fewer studies measuring post-treatment risk. Furthermore, in women with a diagnosis of AIS, post-treatment risk is influenced by the course of treatment; hysterectomy is preferred if women do not wish to maintain fertility, and excisional treatment is used if fertility-sparing treatment is chosen.

(i) Increase in risk

In 119 women treated conservatively using cold-knife conization, LEEP, laser conization, and needle excision and followed up for a mean of 40.9 months, the observed cumulative rate of AIS, CIN, or ICC (adenocarcinoma or squamous cell carcinoma) was 12.6%, whereas no residual disease was observed during the follow-up period in women treated with hysterectomy because of margin involvement in the conization specimen (Costa et al., 2012). Risk of AIS after treatment was included in the above-mentioned study by Swift et al. (2020), of 15 177 women who had undergone treatment for CIN3 or AIS (with LEEP, laser, or conization) in 2006–2010, 509 of whom were treated for AIS, and a 5-year recurrence rate of AIS of 9.0% was observed. A higher recurrence rate was observed in younger women (9.8% in women younger than 45 years compared with 4.9% in women 45 years or older), but this difference was not significant ($P = 0.13$) (Swift et al., 2020).

(ii) Follow-up recommendations for return to screening

For women with a diagnosis of AIS, the recommended post-treatment surveillance protocols depend on whether simple or radical hysterectomy is performed (the preferred treatment) or fertility-sparing treatment is chosen (in patients of reproductive age who wish to preserve the ability to have future pregnancies). Hysterectomy is preferred because AIS is often found in the endocervical canal, which complicates excision; it is often multifocal, which complicates the interpretation of negative margins on the excisional specimen, and biopsy results that indicate AIS warrant an excisional procedure to rule out the presence of invasive adenocarcinoma (Teoh et al., 2020). However, the mean age of diagnosis of AIS is 35–37 years, and women in this age group may wish to have fertility-sparing treatment, which postpones the preferred treatment indefinitely; when childbearing has been completed or is no longer a possibility, hysterectomy is advised.

For women who wish to preserve fertility, post-treatment surveillance after a prior diagnosis of AIS is more intensive than that for HSIL/CIN2+ (Table 5.4). In 2012, the Canadian multi-organization guideline recommended colposcopy, endocervical curettage, and cytology every 6–12 months for at least 5 years, with consideration of hrHPV testing during this period for reassurance [interval not specified]; afterwards, the patient should receive annual cytology testing (Bentley et al., 2012). The Spanish Association of Cervical Pathology and Colposcopy also recommended short-interval testing with colposcopy, cytology, and endocervical sampling for 2 years, and an HPV test at 2 years for TOC, with subsequent HPV testing every 3 years thereafter for women who wish to preserve fertility, if margins are free of disease (AEPCC, 2015).

Although women of reproductive age who wish to preserve fertility may be followed up with intensive surveillance if the excisional specimen (or a re-excisional specimen in cases where negative margins cannot be achieved) has negative margins, fertility-sparing management generally is not recommended (Bentley et al., 2012; Perkins et al., 2020; Teoh et al., 2020). Post-treatment surveillance is most important when the risk of recurrence is high. Localized treatment of AIS has not been shown to decrease the subsequent incidence of invasive adenocarcinoma in women at highest risk of recurrence (Swift et al., 2020).

For women who have undergone fertility-sparing treatment, both the Society of Gynecologic Oncology and ASCCP recommended short-term follow-up with HPV-based testing and endocervical sampling every 6 months for 3 years. If the results are consistently negative, annual HPV-based testing with or without endocervical sampling should be undertaken for 2 years, or until hysterectomy is performed; if test results remain negative, HPV testing should be undertaken every 3 years for at least 25 years, or until hysterectomy is performed (Teoh et al., 2020). For women who have elected to undergo hysterectomy, the initial short-term follow-up consists of annual vaginal HPV-based testing for 3 years, followed by vaginal HPV-based testing every 3 years for at least 25 years, even if testing extends beyond age 65 years (Perkins et al., 2020; Teoh et al., 2020).

5.2.4 Screening of HPV vaccinated populations

(a) The basis for complementary strategies of primary and secondary prevention

HPV vaccination began in earnest in late 2006, 1 year after the publication of the first *IARC Handbook* on cervical cancer screening (IARC, 2005). HPV vaccination was adopted gradually by high-income countries and subsequently by middle- and low-income countries. HPV vaccination is the only evidence-based primary prevention strategy for cervical cancer. At least one of the three approved HPV vaccine formulations (bivalent, quadrivalent, and nonavalent) are currently available in most high-income settings, although the availability is currently limited in LMIC settings (Bruni et al., 2016).

The first results of RCTs on vaccine efficacy were published in 2004 for the bivalent vaccine against HPV types 16 and 18 (Harper et al., 2004) and in 2005 for the quadrivalent vaccine against HPV types 6, 11, 16, and 18 (Villa et al., 2005). Because these vaccines target the two most carcinogenic HPV types that are etiologically linked to cervical cancer (i.e. HPV16 and HPV18), they have the potential to prevent up to 70% of all cervical cancers. The newer nonavalent vaccine (Joura et al., 2015), which targets HPV types 31, 33, 45, 52, and 58 in addition to 6, 11, 16, and 18, has the potential to prevent 90% of all cervical cancers. The screening of future cohorts of vaccinated women has become a complementary policy to accelerate the reduction of cervical cancer incidence to levels below the WHO target of 4 new cases per 100 000 women per year, which is the established threshold to achieve the elimination of cervical cancer as a public health problem (Simms et al., 2019).

(b) Performance of cervical cancer screening in HPV vaccinated populations

Although the two above-mentioned approaches for cervical cancer prevention are clearly complementary, their effects are not simply additive. The interplay between HPV vaccination and cervical cancer screening is complex, because they apply to different periods in a woman's lifetime and because of the different factors that are involved in the health-care system (Fig. 5.2). In spite of these limitations, they can both be viewed as preventive steps in the same continuum in the natural history of cervical cancer.

Fig. 5.2 also illustrates how one strategy (HPV vaccination) influences the performance of the other (cervical cancer screening). For any disease, screening can have clinical value when the condition that needs to be detected is sufficiently common. In the absence of HPV vaccination, the prevalence of CIN is sufficiently high for screening to perform with reasonable accuracy, to enable screening programmes to achieve their intended effect of reducing the incidence of and mortality from cervical cancer with acceptably low risks, such as those stemming from overdiagnosis and harms from overtreatment.

Fig. 5.2 Interplay between primary and secondary prevention strategies for cervical cancer
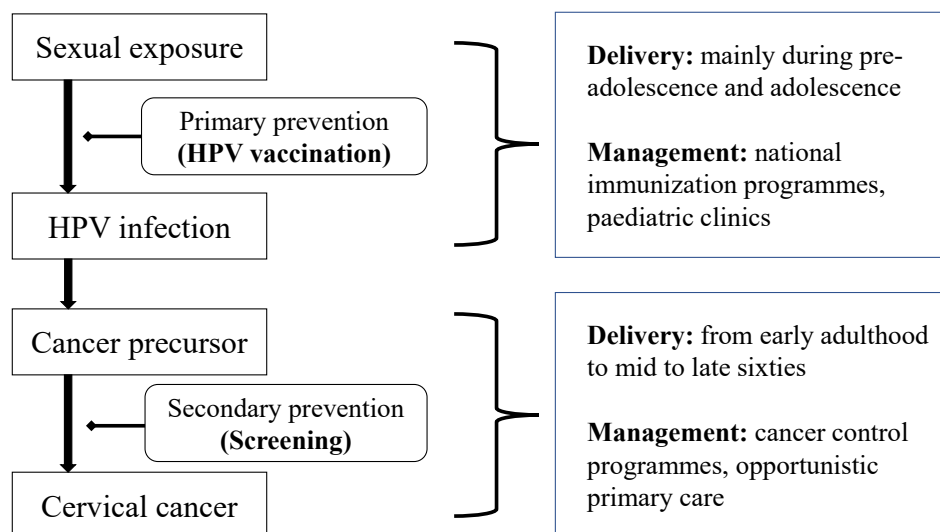
Created by the Working Group.

The simplified trajectory depicted in Fig. 5.2 from the onset of sexual exposure during a woman's late adolescence until the development of cervical cancer, with the highest incidence at ages 40–45 years, implies a long window of opportunity for disease prevention. As successive birth cohorts of vaccinated women reach the age of screening, about 15 years after they were vaccinated, the prevalence of cervical precancerous lesions that can be detected by screening and treated is expected to decrease substantially.

The PPV of cervical cancer screening for detection of CIN2+ is positively correlated with the prevalence of cervical lesions, assuming that test sensitivity and specificity remain unchanged. Therefore, the lower the prevalence of disease, the lower the PPV, and thus there may be a higher proportion of false-positive test results, which may lead to unnecessary diagnostic procedures, such as colposcopies and biopsies, and possible overtreatment. This potential outcome was recognized before HPV vaccination programmes had started, and thus before mass immunization

of girls led to a decrease in the prevalence of cervical precancerous lesions in the first birth cohorts to benefit from HPV vaccines (Franco et al., 2006). The decrease in the PPV of cervical cancer screening after vaccination has been reported in a few populations, mostly those in Australia and in the United Kingdom, which were early adopters of organized, high-coverage HPV vaccination programmes (Palmer et al., 2016; Munro et al., 2017; Sultana et al., 2019).

(c)   Impact of HPV vaccination on screening policies

There has been a steady decrease in the prevalence of vaccine-targeted HPV types and of cervical lesions associated with these types in numerous populations after vaccination (Brotherton et al., 2011; Powell et al., 2012; Baldur-Felskov et al., 2014; Pollock et al., 2014; Carozzi et al., 2016; Cruickshank et al., 2017; Kavanagh et al., 2017; Niccolai et al., 2017; Guo et al., 2018; McGregor et al., 2018; Thamsborg et al., 2018). Infections with HPV16 and HPV18

have become rare in these settings after vaccination (Lynge et al., 2020). Evidence has recently been published that population-based HPV vaccination has decreased the incidence of ICC in Sweden (Lei et al., 2020).

This raises the question of whether high-frequency screening – every 3 years using cytology or every 5 years using HPV testing (irrespective of triage algorithms) – should be sustained. An ancillary question is whether screening should start as early as at age 21 years or 25 years, which is the prevailing policy in many high-resource settings. In many countries that implemented HPV vaccination soon after initial regulatory approval (Australia, Canada, the United Kingdom, and the USA), the first birth cohorts of vaccinated women have now reached age 25 years and are thus being invited to attend screening. In these populations, should screening be started at age 30 years and performed less frequently?

Women who are older than the ages targeted by vaccination programmes fall under the prevailing guidelines for screening frequency. Even in populations targeted by vaccination programmes, participation may be suboptimal because of parental refusal or other reasons that cause people to opt out of vaccination programmes. Therefore, the question of adapting screening algorithms for the entire female population also requires consideration.

Modelling studies have shown that the combination of vaccination and screening is cost-effective and is good value for money, with screening starting later in life – for example at age 30 years for the bivalent or quadrivalent vaccines and at age 35 years for the nonavalent vaccine – and with longer screening intervals (Kim et al., 2017; Pedersen et al., 2018). A related point is that the risk of histologically ascertained precancer after the detection of low-grade abnormalities on cytology has been shown to be much lower in vaccinated women than in unvaccinated women (Castle et al., 2019). [This affects the validity of

current guidelines for managing cervical abnormalities detected by cytology.]

[The expected decrease in the PPV of current screening strategies for detection of CIN2+ after population-based HPV vaccination, and its consequences in terms of potential increased harms from overdiagnosis as well as issues of costs from overscreening or over-referral for colposcopy, apply to all cervical cancer screening tests. However, after vaccination, molecular assays that target nucleic acid sequences of carcinogenic HPV types in cervical samples are a more suitable option than cytology.]

(d) Screening policies for vaccinated women

Only a few countries have considered modifying screening policies in the HPV vaccination era or tailoring guidelines independently for vaccinated and unvaccinated women (Franco et al., 2006; Kim et al., 2017; Pedersen et al., 2018).

In 2012, a consortium led by professional societies and health agencies in the USA reached the conclusion that age-specific screening recommendations should be the same for vaccinated and unvaccinated women (Saslow et al., 2012). At that time, the available vaccines protected only against HPV16 and HPV18, and thus it was expected that about 30% of all cervical cancers would continue to occur. The decision was also made based on the low coverage of HPV vaccination in the USA, which was much lower than the coverage in countries with national vaccination programmes. In addition, the lack of reliable vaccination records implied that physicians could not assume that women who reported having been vaccinated were indeed protected.

The United States Preventive Services Task Force (USPSTF) issued similar recommendations in 2012 for cervical cancer screening irrespective of HPV vaccination status (Moyer et al., 2012). The USPSTF revisited its guidelines in 2018, and the conclusion from a review of the evidence was that the new recommended policies were to be implemented independently of HPV vaccination

status, because the evidence was still insufficient to support a later age to start screening or less frequent screening for vaccinated women (US Preventive Services Task Force, 2018).

The same professional society and health agency stakeholders in the USA that produced the above-mentioned 2012 guidelines (Saslow et al., 2012) reconvened for an update in 2019 (Perkins et al., 2020). Although the focus of the new guidelines was on risk-based management and not on screening algorithms, the recommendation was to omit HPV vaccination status to guide management. This decision was influenced by the low coverage of HPV vaccination in young women, as well as the lack of vaccination registries that would enable clinicians to link primary care records with vaccination histories. Similarly, the 2020 ACS guideline for cervical cancer screening issued recommendations that were independent of vaccination status (Fontham et al., 2020).

A comparable in-depth assessment of the evidence was completed by the Canadian Task Force on Preventive Health Care in 2013. The evidence about the impact that population-based HPV vaccination has on the prevalence of cervical lesions or the incidence of cervical cancer was judged to be insufficient to justify a separate cervical cancer screening policy for vaccinated women (Canadian Task Force on Preventive Health Care, 2013).

To date, only Italy has proposed specific screening policies for vaccinated women since 2017 (Giorgi Rossi et al., 2017). The multi-stakeholder position statement recommended to start screening at age 30 years in vaccinated women, with an HPV test, whereas for unvaccinated women the age to start screening remained at 25 years, with cytology until age 29 years and HPV testing with cytology triage for women aged 30–64 years. The recommendation was based on thresholds of attained risk of CIN3+ for successive birth cohorts of vaccinated women. As risk is maintained at acceptably low levels or decreases

further, the screening interval increases by 1 year for the next birth cohort. At a minimum, the stakeholders defined as essential the adoption of an organized screening programme with high coverage and efficient call–recall, to minimize risks.

As an initial step to modify screening policies in the HPV vaccination era, the Canadian Partnership Against Cancer issued a statement in 2019 recommending that provinces and territories in Canada should stop screening women younger than age 25 years (Popadiuk et al., 2019). The recommendation was based on the high coverage of HPV vaccination in Canada attained since 2007; hence, most young women reaching that age have been protected against the most carcinogenic HPV types (HPV16 and HPV18).

(e) Integration of vaccination and screening

Implementation of HPV testing in screening for cervical cancer enables the accumulation of the evidence needed to inform screening practices. Consistent with the framework shown in Fig. 5.2, it would be helpful for health systems within countries to harmonize their policies on HPV vaccination and screening, with a view to sharing information and resources (Franco et al., 2008). Establishing HPV testing registries with data from women who attend cervical cancer screening and linking the screening data with vaccination registries and cancer registries would provide an efficient surveillance mechanism that would enable the evaluation of the impact of vaccination in reducing the prevalence of carcinogenic HPV types and the incidence of cervical precancerous lesions and cancer (Brotherton et al., 2019). High-level integration of vaccination data and screening data has been shown to work in the state of New Mexico in the USA (Benard et al., 2017).

The integration of planning and systems resources for HPV vaccination and cervical cancer screening has many advantages, in addition to the obvious economy of scale that comes from

Fig. 5.3 Schematic rationale for an ideal integration of vaccination and screening programmes in high-resource settings
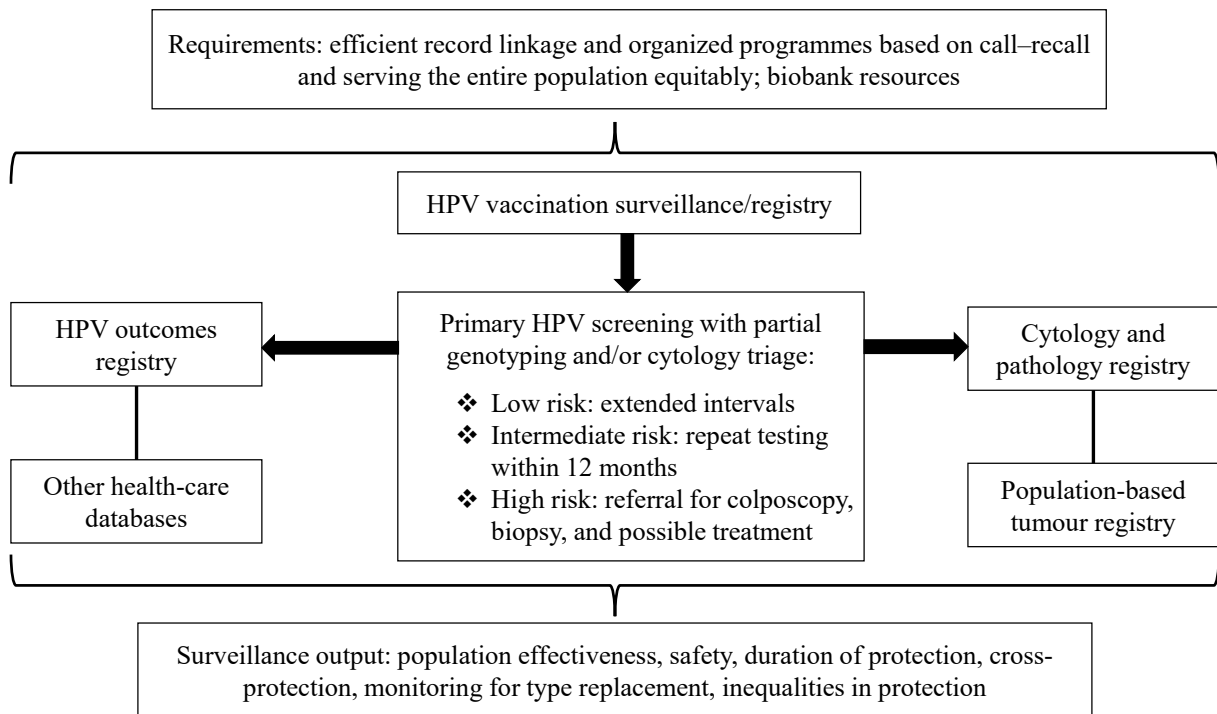
The central component is a generic cervical cancer screening algorithm to inform a surveillance system after vaccination. Not all record linkage components are essential. Efficient epidemiological surveillance can be implemented with a subset of these components.
Created by the Working Group.

centralized procurement of supplies and shared information systems. As shown in Fig. 5.3, for a high-resource setting with centralized cancer control processes, the primary components of this integration are a vaccination registry that provides anonymized identifiers to the screening process, which is a generic screening programme based on a clinically validated HPV test and complemented by a triage algorithm, together with management decisions based on local best practices. Anonymized data generated by the screening programme are linked with administrative health-care databases for cytopathology, colposcopy, treatment outcomes, cancer incidence, and follow-up information. Such integration of processes and data has many dividends for surveillance. As outputs, it is possible to

determine in real time the population-level effectiveness of vaccination, the duration of vaccine protection, and any potential inequalities in the coverage of both vaccination and screening, as well as in their outcomes. An important goal for surveillance is to monitor for possible differences in the coverage of or participation in screening in relation to previous receipt of vaccination. Is there a perception by women who were vaccinated that their risk of cervical cancer is low and therefore they may skip screening visits? A better understanding could be achieved with an integrated system as depicted in Fig. 5.3. Other causes for differences in the coverage or participation, including disparities in access to health care, conscientious objection to vaccination, and refusal to be screened by a male provider, can

be monitored with the linkage system shown in Fig. 5.3.

The addition of a biobank to this integrated system would enable storage of cervical samples for partial HPV genotyping (if this was not already done via the core screening process) or full HPV genotyping. A biobank would also enable more elaborate molecular testing for DNA methylation and other prognostic biomarkers. The availability of genotyping data would enable population-level monitoring of cross-type protection, of herd immunity, and of potential type replacement. The above-mentioned integrated system would also enable the monitoring of the benefits of HPV vaccination in protecting against other HPV-associated cancer types in women. An independent linkage between HPV vaccination registries and cancer registries would also enable assessment of the impact of vaccination on HPV-associated cancer types in men.

Not all of the components shown in Fig. 5.3 are essential for the implementation of an efficient surveillance system with integration of screening and vaccination. Even high-resource regions may not have population-based cancer registries or cytology and pathology registries and may not have established biobanks. Different jurisdictions may decide to implement only the core linkages of vaccination records and screening records, to enable the outcomes of both prevention activities to be monitored.

References

Adamson PC, Huchko MJ, Moss AM, Kinkel HF, Medina-Marino A (2015). Acceptability and accuracy of cervical cancer screening using a self-collected tampon for HPV messenger-RNA testing among HIV-infected women in South Africa. *PLoS One.* 10(9):e0137299. doi:10.1371/journal.pone.0137299 PMID:26332236

AEPCC (2015). Prevention of cervical cancer 2014. Asociación Española de Patología Cervical y Colposcopia. Available from: https://www.aepcc.org/wp-content/uploads/2018/05/AEPCC_revista02_EN_PREVENTION-CC-2014_26032018.pdf.

AIHW (2019). Cervical screening in Australia 2019. Cancer series no. 123. Canberra, Australia: Australian Institute of Health and Welfare. Available from: https://www.aihw.gov.au/reports/cancer-screening/cervical-screening-in-australia-2019/contents/table-of-contents.

Ancelle-Park R, Klein JP, Stroobant A, Smith E, Haikala O, Koch MA, et al. (1993). Expanded European AIDS case definition. *Lancet.* 341(8842):441. doi:10.1016/0140-6736(93)93040-8 PMID:8094208

Anderson JR, Paramsothy P, Heilig C, Jamieson DJ, Shah K, Duerr A; HIV Epidemiology Research (HER) Study Group (2006). Accuracy of Papanicolaou test among HIV-infected women. *Clin Infect Dis.* 42(4):562–8. doi:10.1086/499357 PMID:16421802

Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, et al. (2008). Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst.* 100(9):622–9. doi:10.1093/jnci/djn099 PMID:18445828

Aoki ES, Yin R, Li K, Bhatla N, Singhal S, Ocviyanti D, et al. (2020). National screening programs for cervical cancer in Asian countries. *J Gynecol Oncol.* 31(3):e55. doi:10.3802/jgo.2020.31.e55 PMID:32266804

Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. (2010). European guidelines for quality assurance in cervical cancer screening. Second edition – summary document. *Ann Oncol.* 21(3):448–58. doi:10.1093/annonc/mdp471 PMID:20176693

Arbyn M, Redman CWE, Verdoodt F, Kyrgiou M, Tzafetas M, Ghaem-Maghami S, et al. (2017). Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. *Lancet Oncol.* 18(12):1665–79. doi:10.1016/S1470-2045(17)30700-3 PMID:29126708

Armaroli P, Gallo F, Bellomi A, Ciatto S, Consonni D, Davi D, et al. (2008). Do women ≥ 50 years of age need as much screening as women < 50 years after they have had negative screening results? *Br J Cancer.* 99(2):239–44. doi:10.1038/sj.bjc.6604455 PMID:18594534

Awolude OA, Oyerinde SO (2018). Invasive cervical cancer in Ibadan: socio-sexual characteristics, clinical stage at presentation, histopathology distributions and HIV status. *Afr J Infect Dis.* 13(1):32–8. PMID:30596194

Baldur-Felskov B, Dehlendorff C, Junge J, Munk C, Kjaer SK (2014). Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program. *Cancer Causes Control.* 25(7):915–22. doi:10.1007/s10552-014-0392-4 PMID:24797870

Bansil P, Lim J, Byamugisha J, Kumakech E, Nakisige C, Jeronimo JA (2015). Performance of cervical cancer screening techniques in HIV-infected women in Uganda. *J Low Genit Tract Dis.* 19(3):215–9. doi:10.1097/LGT.0000000000000090 PMID:25551591

Bateman AC, Parham GP, Sahasrabuddhe VV, Mwanahamuntu MH, Kapambwe S, Katundu K, et al. (2014). Clinical performance of digital cervicography and cytology for cervical cancer screening in HIV-infected women in Lusaka, Zambia. *J Acquir Immune Defic Syndr.* 67(2):212–5. doi:10.1097/QAI.0000000000000270 PMID:24977474

Benard VB, Castle PE, Jenison SA, Hunt WC, Kim JJ, Cuzick J, et al.; New Mexico HPV Pap Registry Steering Committee (2017). Population-based incidence rates of cervical intraepithelial neoplasia in the human papillomavirus vaccine era. *JAMA Oncol.* 3(6):833–7. doi:10.1001/jamaoncol.2016.3609 PMID:27685805

Bentley J; Executive Council of the Society of Canadian Colposcopists; Special Contributors (2012). Colposcopic management of abnormal cervical cytology and histology. *J Obstet Gynaecol Can.* 34(12):1188–202. doi:10.1016/S1701-2163(16)35468-8 PMID:23231803

Bhatla N, Singhal S, Saraiya U, Srivastava S, Bhalerao S, Shamsunder S, et al.; FOGSI Expert Group (2020). Screening and management of preinvasive lesions of the cervix: good clinical practice recommendations from the Federation of Obstetrics and Gynaecologic Societies of India (FOGSI). *J Obstet Gynaecol Res.* 46(2):201–14. doi:10.1111/jog.14168 PMID:31814222

Branca M, Rossi E, Alderisio M, Migliore G, Morosini PL, Vecchione A, et al. (2001). Performance of cytology and colposcopy in diagnosis of cervical intraepithelial neoplasia (CIN) in HIV-positive and HIV-negative women. *Cytopathology.* 12(2):84–93. doi:10.1046/j.1365-2303.2001.00299.x PMID:11284952

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 68(6):394–424. doi:10.3322/caac.21492 PMID:30207593

Brotherton JML, Fridman M, May CL, Chappell G, Saville AM, Gertig DM (2011). Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *Lancet.* 377(9783):2085–92. doi:10.1016/S0140-6736(11)60551-5 PMID:21684381

Brotherton JML, Hawkes D, Sultana F, Malloy MJ, Machalek DA, Smith MA, et al. (2019). Age-specific HPV prevalence among 116,052 women in Australia's renewed cervical screening program: a new tool for monitoring vaccine impact. *Vaccine.* 37(3):412–6. doi:10.1016/j.vaccine.2018.11.075 PMID:30551987

Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, et al. (2016). Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. [Erratum in: Lancet Glob Health. 2017 5(7):e662] *Lancet Glob Health.* 4(7):e453–63. doi:10.1016/S2214-109X(16)30099-7 PMID:27340003

Çakmak B, Köseoğlu DR (2014). Comparison of cervical cytological screening results between postmenopausal and elderly women. *Turk Patoloji Derg.* 30(1):38–42. doi:10.5146/tjpath.2014.01163 PMID:24448705

Canadian Task Force on Preventive Health Care (2013). Recommendations on screening for cervical cancer. *CMAJ.* 185(1):35–45. doi:10.1503/cmaj.121505 PMID:23297138

Cancer Council Australia Cervical Cancer Screening Guidelines Working Party (2020). National Cervical Screening Program: guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding. Available from: https://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Screening.

Carozzi FM, Ocello C, Burroni E, Faust H, Zappa M, Paci E, et al. (2016). Effectiveness of HPV vaccination in women reaching screening age in Italy. *J Clin Virol.* 84:74–81. doi:10.1016/j.jcv.2016.09.011 PMID:27728850

Carriero C, Fascilla FD, Cramarossa P, Lepera A, Bettocchi S, Vimercati A (2018). Colpocytological abnormalities in HIV infected and uninfected pregnant women: prevalence, persistence and progression. *J Obstet Gynaecol.* 38(4):526–31. doi:10.1080/01443615.2017.1373082 PMID:29390909

Castañón A, Landy R, Cuzick J, Sasieni P (2014). Cervical screening at age 50–64 years and the risk of cervical cancer at age 65 years and older: population-based case control study. *PLoS Med.* 11(1):e1001585. doi:10.1371/journal.pmed.1001585 PMID:24453946

Castle PE, Xie X, Xue X, Poitras NE, Lorey TS, Kinney WK, et al. (2019). Impact of human papillomavirus vaccination on the clinical meaning of cervical screening results. *Prev Med.* 118:44–50. doi:10.1016/j.ypmed.2018.10.001 PMID:30316878

CDC (1992). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep.* 41(RR-17):1–19. PMID:1361652

Chamot E, Kristensen S, Stringer JSA, Mwanahamuntu MH (2010). Are treatments for cervical precancerous lesions in less-developed countries safe enough to promote scaling-up of cervical screening programs? A systematic review. *BMC Womens Health.* 10(1):11. doi:10.1186/1472-6874-10-11 PMID:20359354

Cherniak W, Tyler N, Arora K, Lapidos-Salaiz I, Sczudlo E, Lin A, et al. (2019). From potential to practice: how accelerating access to HPV tests and screen and treat programmes can help eliminate cervical cancer. *Fam Med Community Health.* 7(4):e000182. doi:10.1136/fmch-2019-000182 PMID:32148728

Cheung LC, Egemen D, Chen X, Katki HA, Demarco M, Wiser AL, et al. (2020). 2019 ASCCP risk-based management consensus guidelines: methods for risk estimation, recommended management, and validation.

J Low Genit Tract Dis. 24(2):90–101. doi:10.1097/LGT.0000000000000528 PMID:32243306

Chibwesha CJ, Frett B, Katundu K, Bateman AC, Shibemba A, Kapambwe S, et al. (2016). Clinical performance validation of 4 point-of-care cervical cancer screening tests in HIV-infected women in Zambia. *J Low Genit Tract Dis*. 20(3):218–23. doi:10.1097/LGT.0000000000000206 PMID:27030883

Chigbu CO, Onyebuchi AK, Nnakenyi EF, Egbuji CC (2017). Impact of visual inspection with acetic acid plus cryotherapy "see and treat" approach on the reduction of the population burden of cervical preinvasive lesions in southeast Nigeria. *Niger J Clin Pract*. 20(2):239–43. doi:10.4103/1119-3077.187315 PMID:28091444

Chin-Hong PV (2016). Human papillomavirus in kidney transplant recipients. *Semin Nephrol*. 36(5):397–404. doi:10.1016/j.semnephrol.2016.05.016 PMID:27772624

Cholli P, Bradford L, Manga S, Nulah K, Kiyang E, Manjuh F, et al. (2018). Screening for cervical cancer among HIV-positive and HIV-negative women in Cameroon using simultaneous co-testing with *care*HPV DNA testing and visual inspection enhanced by digital cervicography: findings of initial screening and one-year follow-up. *Gynecol Oncol*. 148(1):118–25. doi:10.1016/j.ygyno.2017.11.002 PMID:29153541

Chung MH, McKenzie KP, De Vuyst H, Richardson BA, Rana F, Pamnani R, et al. (2013). Comparing Papanicolau smear, visual inspection with acetic acid and human papillomavirus cervical cancer screening methods among HIV-positive women by immune status and antiretroviral therapy. *AIDS*. 27(18):2909–19. doi:10.1097/01.aids.0000432472.92120.1b PMID:23842133

Clarke MA, Unger ER, Zuna R, Nelson E, Darragh TM, Cremer M, et al. (2020). A systematic review of tests for postcolposcopy and posttreatment surveillance. *J Low Genit Tract Dis*. 24(2):148–56. doi:10.1097/LGT.0000000000000526 PMID:32243310

Clifford GM, Gonçalves MAG, Franceschi S; HPV and HIV Study Group (2006). Human papillomavirus types among women infected with HIV: a meta-analysis. *AIDS*. 20(18):2337–44. doi:10.1097/01.aids.0000253361.63578.14 PMID:17117020

Cohn JA, Gagnon S, Spence MR, Harrison DD, Kluzak TR, Langenberg P, et al.; Cervical Disease Study Group of the American Foundation for AIDS Research Community Based Clinical Trials Network (2001). The role of human papillomavirus deoxyribonucleic acid assay and repeated cervical cytologic examination in the detection of cervical intraepithelial neoplasia among human immunodeficiency virus-infected women. *Am J Obstet Gynecol*. 184(3):322–30. doi:10.1067/mob.2001.109938 PMID:11228481

Costa S, Venturoli S, Negri G, Sideri M, Preti M, Pesaresi M, et al. (2012). Factors predicting the outcome of conservatively treated adenocarcinoma in situ of the uterine cervix: an analysis of 166 cases. *Gynecol Oncol*. 124(3):490–5. doi:10.1016/j.ygyno.2011.11.039 PMID:22188786

Cruickshank ME, Pan J, Cotton SC, Kavanagh K, Robertson C, Cuschieri K, et al. (2017). Reduction in colposcopy workload and associated clinical activity following human papillomavirus (HPV) catch-up vaccination programme in Scotland: an ecological study. *BJOG*. 124(9):1386–93. doi:10.1111/1471-0528.14562 PMID:28102928

Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al.; US Preventive Services Task Force (2018). Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 320(7):674–86. doi:10.1001/jama.2018.10897 PMID:30140884

Darlin L, Borgfeldt C, Widén E, Kannisto P (2014). Elderly women above screening age diagnosed with cervical cancer have a worse prognosis. *Anticancer Res*. 34(9):5147–51. PMID:25202106

Davis M, Perkins R, Cain J, Feldman S (2016). Cervical cancer screening and the immunosuppressed patient: the issues in screening high-risk populations. *Curr Obstet Gynecol Rep*. 5(4):307–17. doi:10.1007/s13669-016-0180-0

De Vuyst H, Lillo F, Broutet N, Smith JS (2008). HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. *Eur J Cancer Prev*. 17(6):545–54. doi:10.1097/CEJ.0b013e3282f75ea1 PMID:18941376

Demarco M, Egemen D, Raine-Bennett TR, Cheung LC, Befano B, Poitras NE, et al. (2020). A study of partial human papillomavirus genotyping in support of the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis*. 24(2):144–7. doi:10.1097/LGT.0000000000000530 PMID:32243309

Denny L, de Sanjose S, Mutebi M, Anderson BO, Kim J, Jeronimo J, et al. (2017). Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. *Lancet*. 389(10071):861–70. doi:10.1016/S0140-6736(16)31795-0 PMID:27814963

Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright TC Jr (2005). Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA*. 294(17):2173–81. doi:10.1001/jama.294.17.2173 PMID:16264158

Denslow SA, Rositch AF, Firnhaber C, Ting J, Smith JS (2014). Incidence and progression of cervical lesions in women with HIV: a systematic global review. *Int J STD AIDS*. 25(3):163–77. doi:10.1177/0956462413491735 PMID:24216030

Díaz del Arco C, Jiménez Ayala B, García D, Sanabria C, Fernández Aceñero MJ (2019). Distribution of cervical lesions in young and older women. *Diagn Cytopathol*. 47(7):659–64. doi:10.1002/dc.24163 PMID:31184808

Dolman L, Sauvaget C, Muwonge R, Sankaranarayanan R (2014). Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review. *BJOG*. 121(8):929–42. doi:10.1111/1471-0528.12655 PMID:24597779

Dowling EC, Klabunde C, Patnick J, Ballard-Barbash R; International Cancer Screening Network (ICSN) (2010). Breast and cervical cancer screening programme implementation in 16 countries. *J Med Screen*. 17(3):139–46. doi:10.1258/jms.2010.010033 PMID:20956724

Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, Efstathiou JA, Grover S, Chiyapo S, et al. (2016). HIV infection and survival among women with cervical cancer. *J Clin Oncol*. 34(31):3749–57. doi:10.1200/JCO.2016.67.9613 PMID:27573661

Dube Mandishora RS, Christiansen IK, Chin'ombe N, Duri K, Ngara B, Rounge TB, et al. (2017). Genotypic diversity of anogenital human papillomavirus in women attending cervical cancer screening in Harare, Zimbabwe. *J Med Virol*. 89(9):1671–7. doi:10.1002/jmv.24825 PMID:28390142

Egemen D, Cheung LC, Chen X, Demarco M, Perkins RB, Kinney W, et al. (2020). Risk estimates supporting the 2019 ASCCP risk-based management consensus guidelines. *J Low Genit Tract Dis*. 24(2):132–43. doi:10.1097/LGT.0000000000000529 PMID:32243308

Elliott T, Kohler RE, Monare B, Moshashane N, Ramontshonyana K, Muthoga C, et al. (2019). Performance of vaginal self-sampling for human papillomavirus testing among women living with HIV in Botswana. *Int J STD AIDS*. 30(12):1169–76. doi:10.1177/0956462419868618 PMID:31558129

Ermel AC, Fife KH (2016). Human papillomavirus DNA detection in older women – implications for cancer screening and prevention. *J Infect Dis*. 214(5):657–8. doi:10.1093/infdis/jiw075 PMID:27009603

Ezechi OC, Odberg Petterson K, Gbajabiamila TA, Idigbe IE, Gab-Okafor CV, Okolo CA, et al. (2016). Evaluation of direct visual inspection of the cervix in detecting cytology diagnosed squamous intraepithelial lesion in women of known HIV status. a randomized trial (CANHIV study). *Afr J Reprod Health*. 20(4):77–88. doi:10.29063/ajrh2016/v20i4.8 PMID:29566322

Firnhaber C, Mayisela N, Mao L, Williams S, Swarts A, Faesen M, et al. (2013). Validation of cervical cancer screening methods in HIV positive women from Johannesburg South Africa. *PLoS One*. 8(1):e53494. doi:10.1371/journal.pone.0053494 PMID:23326441

Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, et al. (2020). Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 70(5):321–46. doi:10.3322/caac.21628 PMID:32729638

Franco EL, Cuzick J, Hildesheim A, de Sanjosé S (2006). Chapter 20: issues in planning cervical cancer screening in the era of HPV vaccination. *Vaccine*. 24(Suppl 3):S171–7. doi:10.1016/j.vaccine.2006.05.061 PMID:16844268

Franco EL, Tsu V, Herrero R, Lazcano-Ponce E, Hildesheim A, Muñoz N, et al. (2008). Integration of human papillomavirus vaccination and cervical cancer screening in Latin America and the Caribbean. *Vaccine*. 26(Suppl 11):L88–95. doi:10.1016/j.vaccine.2008.05.026 PMID:18945406

Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP (2007). Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol*. 8(11):985–93. doi:10.1016/S1470-2045(07)70283-8 PMID:17928267

Gichangi PB, Bwayo J, Estambale B, De Vuyst H, Ojwang S, Rogo K, et al. (2003). Impact of HIV infection on invasive cervical cancer in Kenyan women. *AIDS*. 17(13):1963–8. doi:10.1097/00002030-200309050-00015 PMID:12960829

Giorgi Rossi P, Carozzi F, Federici A, Ronco G, Zappa M, Franceschi S, et al.; Italian Screening in HPV vaccinated girls Consensus Conference group (2017). Cervical cancer screening in women vaccinated against human papillomavirus infection: recommendations from a consensus conference. *Prev Med*. 98:21–30. doi:10.1016/j.ypmed.2016.11.020 PMID:27894910

Giorgi-Rossi P, Franceschi S, Ronco G (2012). HPV prevalence and accuracy of HPV testing to detect high-grade cervical intraepithelial neoplasia. *Int J Cancer*. 130(6):1387–94. doi:10.1002/ijc.26147 PMID:21520039

Grainge MJ, Seth R, Guo L, Neal KR, Coupland C, Vryenhoef P, et al. (2005). Cervical human papillomavirus screening among older women. *Emerg Infect Dis*. 11(11):1680–5. doi:10.3201/eid1111.050575 PMID:16318718

Gravitt PE, Landy R, Schiffman M (2018). How confident can we be in the current guidelines for exiting cervical screening? *Prev Med*. 114:188–92. doi:10.1016/j.ypmed.2018.07.005 PMID:29981791

Greene SA, De Vuyst H, John-Stewart GC, Richardson BA, McGrath CJ, Marson KG, et al. (2019). Effect of cryotherapy vs loop electrosurgical excision procedure on cervical disease recurrence among women with HIV and high-grade cervical lesions in Kenya: a randomized clinical trial. *JAMA*. 322(16):1570–9. doi:10.1001/jama.2019.14969 PMID:31638680

Guo F, Cofie LE, Berenson AB (2018). Cervical cancer incidence in young US females after human papillomavirus vaccine introduction. *Am J Prev Med*. 55(2):197–204. doi:10.1016/j.amepre.2018.03.013 PMID:29859731

Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al.; GlaxoSmithKline HPV Vaccine Study Group (2004). Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human

papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*. 364(9447):1757–65. doi:10.1016/S0140-6736(04)17398-4 PMID:15541448

Holcomb K, Maiman M, Dimaio T, Gates J (1998). Rapid progression to invasive cervix cancer in a woman infected with the human immunodeficiency virus. *Obstet Gynecol*. 91(5 Pt 2):848–50. doi:10.1016/S0029-7844(97)00607-8 PMID:9572187

Huchko MJ, Sneden J, Leslie HH, Abdulrahim N, Maloba M, Bukusi E, et al. (2014). A comparison of two visual inspection methods for cervical cancer screening among HIV-infected women in Kenya. *Bull World Health Organ*. 92(3):195–203. doi:10.2471/BLT.13.122051 PMID:24700979

Huchko MJ, Sneden J, Zakaras JM, Smith-McCune K, Sawaya G, Maloba M, et al. (2015). A randomized trial comparing the diagnostic accuracy of visual inspection with acetic acid to visual inspection with Lugol's iodine for cervical cancer screening in HIV-infected women. *PLoS One*. 10(4):e0118568. doi:10.1371/journal.pone.0118568 PMID:25849627

IARC (2005). Cervix cancer screening. *IARC Handb Cancer Prev*. 10:1–302. Available from: https://publications.iarc.fr/380.

INCa (2019). Surveillance post-thérapeutique des lésions précancéreuses du col de l'utérus/thésaurus. Boulogne-Billancourt, France: French National Cancer Institute (INCa). [in French] Available from: https://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Thesaurus-Surveillance-post-therapeutique-des-lesions-precancereuses-du-col-de-l-uterus.

Joshi S, Sankaranarayanan R, Muwonge R, Kulkarni V, Somanathan T, Divate U (2013). Screening of cervical neoplasia in HIV-infected women in India. *AIDS*. 27(4):607–15. doi:10.1097/QAD.0b013e32835b1041 PMID:23079814

Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al.; Broad Spectrum HPV Vaccine Study (2015). A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 372(8):711–23. doi:10.1056/NEJMoa1405044 PMID:25693011

Kalliala I, Anttila A, Pukkala E, Nieminen P (2005). Risk of cervical and other cancers after treatment of cervical intraepithelial neoplasia: retrospective cohort study. *BMJ*. 331(7526):1183–5. doi:10.1136/bmj.38663.459039.7C PMID:16293840

Kalliala I, Athanasiou A, Veroniki AA, Salanti G, Efthimiou O, Raftis N, et al. (2020). Incidence and mortality from cervical cancer and other malignancies after treatment of cervical intraepithelial neoplasia: a systematic review and meta-analysis of the literature. *Ann Oncol*. 31(2):213–27. doi:10.1016/j.annonc.2019.11.004 PMID:31959338

Kamineni A, Weinmann S, Shy KK, Glass AG, Weiss NS (2013). Efficacy of screening in preventing cervical cancer among older women. *Cancer Causes Control*. 24(9):1653–60. doi:10.1007/s10552-013-0239-4 PMID:23744043

Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T, et al. (2013). Five-year risk of recurrence after treatment of CIN 2, CIN 3, or AIS: performance of HPV and Pap cotesting in posttreatment management. *J Low Genit Tract Dis*. 17(5 Suppl 1):S78–84. doi:10.1097/LGT.0b013e31828543c5 PMID:23519309

Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. (2017). Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. *Lancet Infect Dis*. 17(12):1293–302. doi:10.1016/S1473-3099(17)30468-1 PMID:28965955

Kelly H, Weiss HA, Benavente Y, de Sanjose S, Mayaud P, Qiao Y, et al.; ART and HPV Review Group (2018). Association of antiretroviral therapy with high-risk human papillomavirus, cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis. *Lancet HIV*. 5(1):e45–58. doi:10.1016/S2352-3018(17)30149-2 PMID:29107561

Kim SC, Feldman S, Moscicki AB (2018). Risk of human papillomavirus infection in women with rheumatic disease: cervical cancer screening and prevention. *Rheumatology (Oxford)*. 57(Suppl 5):v26–33. doi:10.1093/rheumatology/kex523 PMID:30137592

Kim JJ, Burger EA, Sy S, Campos NG (2017). Optimal cervical cancer screening in women vaccinated against human papillomavirus. *J Natl Cancer Inst*. 109(2):djw216. doi:10.1093/jnci/djw216 PMID:27754955

Kitchener H, Nelson L, Adams J, Mesher D, Sasieni P, Cubie H, et al. (2007). Colposcopy is not necessary to assess the risk to the cervix in HIV-positive women: an international cohort study of cervical pathology in HIV-1 positive women. *Int J Cancer*. 121(11):2484–91. doi:10.1002/ijc.22947 PMID:17683070

Kremer WW, van Zummeren M, Breytenbach E, Richter KL, Steenbergen RDM, Meijer CJLM, et al. (2019). The use of molecular markers for cervical screening of women living with HIV in South Africa. *AIDS*. 33(13):2035–42. doi:10.1097/QAD.0000000000002325 PMID:31385866

Kuhn L, Saidu R, Boa R, Tergas A, Moodley J, Persing D, et al. (2020). Clinical evaluation of modifications to a human papillomavirus assay to optimise its utility for cervical cancer screening in low-resource settings: a diagnostic accuracy study. *Lancet Glob Health*. 8(2):e296–304. doi:10.1016/S2214-109X(19)30527-3 PMID:31981559

Kuhn L, Wang C, Tsai WY, Wright TC, Denny L (2010). Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women. *AIDS*. 24(16):2553–61. doi:10.1097/QAD.0b013e32833e163e PMID:20706107

Kulasingam SL, Havrilesky LJ, Ghebre R, Myers ER (2013). Screening for cervical cancer: a modeling study for the US Preventive Services Task Force. *J Low Genit Tract Dis*. 17(2):193–202. doi:10.1097/LGT.0b013e3182616241 PMID:23519288

Landy R, Schiffman M, Sasieni PD, Cheung LC, Katki HA, Rydzak G, et al. (2020). Absolute risks of cervical precancer among women who fulfill exiting guidelines based on HPV and cytology cotesting. *Int J Cancer*. 146(3):617–26. doi:10.1002/ijc.32268 PMID:30861114

Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. (2020). HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med*. 383(14):1340–8. doi:10.1056/NEJMoa1917338 PMID:32997908

Liu G, Sharma M, Tan N, Barnabas RV (2018). HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. *AIDS*. 32(6):795–808. doi:10.1097/QAD.0000000000001765 PMID:29369827

Lönnberg S, Nieminen P, Luostarinen T, Anttila A (2013). Mortality audit of the Finnish cervical cancer screening program. *Int J Cancer*. 132(9):2134–40. doi:10.1002/ijc.27844 PMID:22987437

Looker KJ, Rönn MM, Brock PM, Brisson M, Drolet M, Mayaud P, et al. (2018). Evidence of synergistic relationships between HIV and human papillomavirus (HPV): systematic reviews and meta-analyses of longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status. *J Int AIDS Soc*. 21(6):e25110. doi:10.1002/jia2.25110 PMID:29873885

Luckett R, Mogowa N, Li HJ, Erlinger A, Hacker MR, Esselen K, et al. (2019). Performance of two-stage cervical cancer screening with primary high-risk human papillomavirus testing in women living with human immunodeficiency virus. *Obstet Gynecol*. 134(4):840–9. doi:10.1097/AOG.0000000000003496 PMID:31503167

Lynge E, Thamsborg L, Larsen LG, Christensen J, Johansen T, Hariri J, et al. (2020). Prevalence of high-risk human papillomavirus after HPV-vaccination in Denmark. *Int J Cancer*. 147(12):3446–52. doi:10.1002/ijc.33157 PMID:32542644

Mabeya H, Khozaim K, Liu T, Orango O, Chumba D, Pisharodi L, et al. (2012). Comparison of conventional cervical cytology versus visual inspection with acetic acid among human immunodeficiency virus-infected women in western Kenya. *J Low Genit Tract Dis*. 16(2):92–7. doi:10.1097/LGT.0b013e3182320f0c PMID:22126834

Maiman M, Fruchter RG, Sedlis A, Feldman J, Chen P, Burk RD, et al. (1998). Prevalence, risk factors, and accuracy of cytologic screening for cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Gynecol Oncol*. 68(3):233–9. doi:10.1006/gyno.1998.4938 PMID:9570972

Malagón T, Kulasingam S, Mayrand MH, Ogilvie G, Smith L, Bouchard C, et al. (2018). Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated women: a modelling study. *Lancet Oncol*. 19(12):1569–78. doi:10.1016/S1470-2045(18)30536-9 PMID:30392810

Martin CE, Tergas AI, Wysong M, Reinsel M, Estep D, Varallo J (2014). Evaluation of a single-visit approach to cervical cancer screening and treatment in Guyana: feasibility, effectiveness and lessons learned. *J Obstet Gynaecol Res*. 40(6):1707–16. doi:10.1111/jog.12366 PMID:24888938

Massad LS, Hessol NA, Darragh TM, Minkoff H, Colie C, Wright RL, et al. (2017). Cervical cancer incidence after up to 20 years of observation among women with HIV. *Int J Cancer*. 141(8):1561–5. doi:10.1002/ijc.30866 PMID:28670714

Maza M, Figueroa R, Laskow B, Juárez A, Alfaro K, Alonzo TA, et al. (2018). Effects of maintenance on quality of performance of cryotherapy devices for treatment of precancerous cervical lesions. *J Low Genit Tract Dis*. 22(1):47–51. doi:10.1097/LGT.0000000000000359 PMID:29271857

Mbulawa ZZA, Coetzee D, Williamson AL (2015). Human papillomavirus prevalence in South African women and men according to age and human immunodeficiency virus status. *BMC Infect Dis*. 15(1):459–459. doi:10.1186/s12879-015-1181-8 PMID:26502723

Mbulawa ZZA, Wilkin TJ, Goeieman B, Swarts A, Williams S, Levin S, et al. (2016). Xpert human papillomavirus test is a promising cervical cancer screening test for HIV-seropositive women. *Papillomavirus Res*. 2:56–60. doi:10.1016/j.pvr.2016.02.004 PMID:29074186

McGregor S, Saulo D, Brotherton JML, Liu B, Phillips S, Skinner SR, et al. (2018). Decline in prevalence of human papillomavirus infection following vaccination among Australian Indigenous women, a population at higher risk of cervical cancer: the VIP-I study. *Vaccine*. 36(29):4311–6. doi:10.1016/j.vaccine.2018.05.104 PMID:29880245

Ministry of Health New Zealand (2020). Clinical practice guidelines for cervical screening in New Zealand 2020. Wellington, New Zealand: Ministry of Health. Available from: https://www.nsu.govt.nz/system/files/resources/final_ncsp-guidelines-for-cervical-screening-new-zealand-5_june_2020.pdf.

Moodley M, Moodley J, Kleinschmidt I (2001). Invasive cervical cancer and human immunodeficiency virus (HIV) infection: a South African perspective. *Int*

J Gynecol Cancer. 11(3):194–7. doi:10.1046/j.1525-1438.2001.01022.x PMID:11437924

Moscicki AB, Ellenberg JH, Farhat S, Xu J (2004). Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. *J Infect Dis*. 190(1):37–45. doi:10.1086/421467 PMID:15195241

Moscicki AB, Flowers L, Huchko MJ, Long ME, MacLaughlin KL, Murphy J, et al. (2019). Guidelines for cervical cancer screening in immunosuppressed women without HIV infection. *J Low Genit Tract Dis*. 23(2):87–101. doi:10.1097/LGT.0000000000000468 PMID:30907775

Moyer VA; U.S. Preventive Services Task Force (2012). Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 156(12):880–91. doi:10.7326/0003-4819-156-12-201206190-00424 PMID:22711081

Munro A, Gillespie C, Cotton S, Busby-Earle C, Kavanagh K, Cuschieri K, et al. (2017). The impact of human papillomavirus type on colposcopy performance in women offered HPV immunisation in a catch-up vaccine programme: a two-centre observational study. *BJOG*. 124(9):1394–401. doi:10.1111/1471-0528.14563 PMID:28102931

National Department of Health South Africa (2020). Cervical cancer prevention and control policy, South Africa, 2019. Pretoria, South Africa: National Department of Health. Available from: https://cansa.org.za/files/2021/03/cervical_cancer_prevention_and_control_policy.pdf.

Ndizeye Z, Menon S, Van Geertruyden JP, Sauvaget C, Jacquemyn Y, Bogers JP, et al. (2019). Performance of OncoE6™ Cervical Test in detecting cervical precancer lesions in HIV-positive women attending an HIV clinic in Bujumbura, Burundi: a cross-sectional study. *BMJ Open*. 9(9):e029088. doi:10.1136/bmjopen-2019-029088 PMID:31494606

Ngou J, Gilham C, Omar T, Goumbri-Lompo O, Doutre S, Michelow P, et al. (2015). Comparison of analytical and clinical performances of the Digene HC2 HPV DNA assay and the INNO-LiPA HPV genotyping assay for detecting high-risk HPV infection and cervical neoplasia among HIV-positive African women. *J Acquir Immune Defic Syndr*. 68(2):162–8. doi:10.1097/QAI.0000000000000428 PMID:25394189

Ngou J, Magooa MP, Gilham C, Djigma F, Didelot MN, Kelly H, et al.; HARP Study Group (2013). Comparison of *care*HPV and Hybrid Capture 2 assays for detection of high-risk human papillomavirus DNA in cervical samples from HIV-1-infected African women. *J Clin Microbiol*. 51(12):4240–2. doi:10.1128/JCM.02144-13 PMID:24108613

Niccolai LM, Meek JI, Brackney M, Hadler JL, Sosa LE, Weinberger DM (2017). Declines in human papillomavirus (HPV)-associated high-grade cervical lesions after introduction of HPV vaccines in Connecticut, United States, 2008–2015. *Clin Infect Dis*. 65(6):884–9. doi:10.1093/cid/cix455 PMID:28520854

NordScreen (2017). Cancer screening fact sheet: Sweden – cervix – 2017. Stockholm, Sweden: Department of Laboratory Medicine, Karolinska Institutet. Available from: https://nordscreen.org/wp-content/uploads/2017/05/Cervix-Fact-Sheet-Sweden-2017.pdf.

Obiri-Yeboah D, Adu-Sarkodie Y, Djigma F, Hayfron-Benjamin A, Abdul L, Simpore J, et al. (2017). Self-collected vaginal sampling for the detection of genital human papillomavirus (HPV) using *care*HPV among Ghanaian women. *BMC Womens Health*. 17(1):86. doi:10.1186/s12905-017-0448-1 PMID:28950841

Palefsky JM (2017). Human papillomavirus-associated anal and cervical cancers in HIV-infected individuals: incidence and prevention in the antiretroviral therapy era. *Curr Opin HIV AIDS*. 12(1):26–30. doi:10.1097/COH.0000000000000336 PMID:27828801

Palmer TJ, McFadden M, Pollock KGJ, Kavanagh K, Cuschieri K, Cruickshank M, et al. (2016). HPV immunisation and cervical screening – confirmation of changed performance of cytology as a screening test in immunised women: a retrospective population-based cohort study. *Br J Cancer*. 114(5):582–9. doi:10.1038/bjc.2015.474 PMID:26931370

Pankakoski M, Anttila A, Sarkeala T, Heinävaara S (2019). Effectiveness of cervical cancer screening at age 65 – a register-based cohort study. *PLoS One*. 14(3):e0214486. doi:10.1371/journal.pone.0214486 PMID:30913262

Pankakoski M, Heinävaara S, Anttila A, Sarkeala T (2020). Differences in cervical test coverage by age, socioeconomic status, ethnic origin and municipality type – a nationwide register-based study. *Prev Med*. 139:106219. doi:10.1016/j.ypmed.2020.106219 PMID:32693176

Parham GP, Mwanahamuntu MH, Sahasrabuddhe VV, Westfall AO, King KE, Chibwesha C, et al. (2010). Implementation of cervical cancer prevention services for HIV-infected women in Zambia: measuring program effectiveness. *HIV Ther*. 4(6):713–22. doi:10.2217/hiv.10.52 PMID:25419240

Pedersen K, Burger EA, Nygård M, Kristiansen IS, Kim JJ (2018). Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: the value of stratifying guidelines. *Eur J Cancer*. 91:68–75. doi:10.1016/j.ejca.2017.12.018 PMID:29335156

Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al.; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee (2020). 2019 ASCCP Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors. [Erratum in: J Low Genit Tract Dis. 2021 25(4):330–1] *J Low Genit Tract Dis*. 24(2):102–31. doi:10.1097/LGT.0000000000000525 PMID:32243307

Petignat P, Hankins C, Walmsley S, Money D, Provencher D, Pourreaux K, et al.; Canadian Women's HIV Study Group (2005). Self-sampling is associated with increased detection of human papillomavirus DNA in the genital tract of HIV-seropositive women. *Clin Infect Dis*. 41(4):527–34. doi:10.1086/432059 PMID:16028163

Phanuphak N, Teeraananchai S, Hansudewechakul R, Gatechompol S, Chokephaibulkit K, Dang HLD, et al. (2020). Incidence and persistence of high-risk anogenital human papillomavirus infection among female youth with and without perinatally acquired HIV infection: a 3-year observational cohort study. *Clin Infect Dis*. 71(8):e270–80. doi:10.1093/cid/ciz1143 PMID:31768522

Pinder LF, Parham GP, Basu P, Muwonge R, Lucas E, Nyambe N, et al. (2020). Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial. *Lancet Oncol*. 21(1):175–84. doi:10.1016/S1470-2045(19)30635-7 PMID:31734069

Pollock KGJ, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, et al. (2014). Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *Br J Cancer*. 111(9):1824–30. doi:10.1038/bjc.2014.479 PMID:25180766

Popadiuk C, Decker K, Gauvreau C (2019). Starting cervical cancer screening at 25 years of age: the time has come. *CMAJ*. 191(1):E1–2. doi:10.1503/cmaj.181312 PMID:30617226

Powell SE, Hariri S, Steinau M, Bauer HM, Bennett NM, Bloch KC, et al. (2012). Impact of human papillomavirus (HPV) vaccination on HPV 16/18-related prevalence in precancerous cervical lesions. *Vaccine*. 31(1):109–13. doi:10.1016/j.vaccine.2012.10.092 PMID:23137842

Public Health England (2016). NHS Cervical Screening Programme: colposcopy and programme management. 3rd ed. London, UK: Public Health England. Available from: https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management.

Public Health England (2020). NHS cervical screening (CSP) programme. London, UK: Public Health England. Available from: https://www.gov.uk/health-and-social-care/population-screening-programmes-cervical.

Randall TC, Sauvaget C, Muwonge R, Trimble EL, Jeronimo J (2019). Worthy of further consideration: an updated meta-analysis to address the feasibility, acceptability, safety and efficacy of thermal ablation in the treatment of cervical cancer precursor lesions. *Prev Med*. 118:81–91. doi:10.1016/j.ypmed.2018.10.006 PMID:30342109

Rellihan MA, Dooley DP, Burke TW, Berkland ME, Longfield RN (1990). Rapidly progressing cervical cancer in a patient with human immunodeficiency virus infection. *Gynecol Oncol*. 36(3):435–8. doi:10.1016/0090-8258(90)90159-I PMID:2318457

RIVM (2020). Cervical cancer screening programme. Bilthoven, Netherlands: National Institute for Public Health and the Environment (RIVM). Available from: https://www.rivm.nl/en/cervical-cancer-screening-programme.

Rohner E, Bütikofer L, Schmidlin K, Sengayi M, Maskew M, Giddy J, et al. (2020). Cervical cancer risk in women living with HIV across four continents: a multicohort study. *Int J Cancer*. 146(3):601–9. doi:10.1002/ijc.32260 PMID:31215037

Rohner E, Sengayi M, Goeieman B, Michelow P, Firnhaber C, Maskew M, et al. (2017). Cervical cancer risk and impact of Pap-based screening in HIV-positive women on antiretroviral therapy in Johannesburg, South Africa. *Int J Cancer*. 141(3):488–96. doi:10.1002/ijc.30749 PMID:28440019

Roser M, Ritchie H (2019). HIV/AIDS. Published online at OurWorldInData.org. Available from: https://ourworldindata.org/hiv-aids.

Rositch AF, Burke AE, Viscidi RP, Silver MI, Chang K, Gravitt PE (2012). Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women. *Cancer Res*. 72(23):6183–90. doi:10.1158/0008-5472.CAN-12-2635 PMID:23019223

Rositch AF, Silver MI, Gravitt PE (2014). Cervical cancer screening in older women: new evidence and knowledge gaps. *PLoS Med*. 11(1):e1001586. doi:10.1371/journal.pmed.1001586 PMID:24453947

Rudd P, Gorman D, Meja S, Mtonga P, Jere Y, Chidothe I, et al. (2017). Cervical cancer in southern Malawi: a prospective analysis of presentation, management, and outcomes. *Malawi Med J*. 29(2):124–9. doi:10.4314/mmj.v29i2.9 PMID:28955419

Saccucci P, Mastrone M, Are P, Pisani G, Provenza C (1996). Rapidly progressive squamous cell carcinoma of the cervix in a patient with acquired immunodeficiency syndrome: case report. *Eur J Gynaecol Oncol*. 17(4):306–8. PMID:8856313

Safaeian M, Kiddugavu M, Gravitt PE, Ssekasanvu J, Murokora D, Sklar M, et al. (2007). Comparability of self-collected vaginal swabs and physician-collected cervical swabs for detection of human papillomavirus infections in Rakai, Uganda. *Sex Transm Dis*. 34(7):429–36. doi:10.1097/01.olq.0000243623.67673.22 PMID:17075437

Sahasrabuddhe VV, Bhosale RA, Kavatkar AN, Nagwanshi CA, Joshi SN, Jenkins CA, et al. (2012). Comparison of visual inspection with acetic acid and cervical cytology to detect high-grade cervical neoplasia among

HIV-infected women in India. *Int J Cancer*. 130(1):234–40. doi:10.1002/ijc.25971 PMID:21387289

Sandoval M, Slavkovsky R, Bansil P, Jeronimo J, Lim J, Figueroa J, et al. (2019). Acceptability and safety of thermal ablation for the treatment of precancerous cervical lesions in Honduras. *Trop Med Int Health*. 24(12):1391–9. doi:10.1111/tmi.13315 PMID:31622526

Sankaranarayanan R, Rajkumar R, Esmy PO, Fayette JM, Shanthakumary S, Frappart L, et al. (2007). Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer*. 96:738–43. doi:10.1038/sj.bjc.6603633 PMID:17311015

Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, et al. (2016). Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. *Int J Gynaecol Obstet*. 132(3):266–71. doi:10.1016/j.ijgo.2015.07.026 PMID:26643302

Sasieni P, Adams J, Cuzick J (2003). Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *Br J Cancer*. 89(1):88–93. doi:10.1038/sj.bjc.6600974 PMID:12838306

Sasieni P, Castanon A, Cuzick J (2009). Effectiveness of cervical screening with age: population-based case-control study of prospectively recorded data. *BMJ*. 339:b2968. doi:10.1136/bmj.b2968 PMID:19638651

Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al.; ACS-ASCCP-ASCP Cervical Cancer Guideline Committee (2012). American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin*. 62(3):147–72. doi:10.3322/caac.21139 PMID:22422631

Schiffman M, Doorbar J, Wentzensen N, de Sanjosé S, Fakhry C, Monk BJ, et al. (2016). Carcinogenic human papillomavirus infection. *Nat Rev Dis Primers*. 2(1):16086. doi:10.1038/nrdp.2016.86 PMID:27905473

Schiffman M, Wentzensen N, Perkins RB, Guido RS (2020). An introduction to the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis*. 24(2):87–9. doi:10.1097/LGT.0000000000000531 PMID:32243305

Segondy M, Kelly H, Magooa MP, Djigma F, Ngou J, Gilham C, et al.; HARP Study Group (2016). Performance of *care*HPV for detecting high-grade cervical intraepithelial neoplasia among women living with HIV-1 in Burkina Faso and South Africa: HARP study. *Br J Cancer*. 115(4):425–30. doi:10.1038/bjc.2016.207 PMID:27434037

Sigfrid L, Murphy G, Haldane V, Chuah FLH, Ong SE, Cervero-Liceras F, et al. (2017). Integrating cervical cancer with HIV healthcare services: a systematic review. *PLoS One*. 12(7):e0181156. doi:10.1371/journal.pone.0181156 PMID:28732037

Simms KT, Steinberg J, Caruana M, Smith MA, Lew JB, Soerjomataram I, et al. (2019). Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020–99: a modelling study. *Lancet Oncol*. 20(3):394–407. doi:10.1016/S1470-2045(18)30836-2 PMID:30795950

Soutter WP, de Barros Lopes A, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. (1997). Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet*. 349(9057):978–80. doi:10.1016/S0140-6736(96)08295-5 PMID:9100623

Soutter WP, Sasieni P, Panoskaltsis T (2006). Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer*. 118(8):2048–55. doi:10.1002/ijc.21604 PMID:16284947

Starks D, Arriba LN, Enerson CL, Brainard J, Nagore N, Chiesa-Vottero A, et al. (2014). Mexican Cervical Cancer Screening Study II: 6-month and 2-year follow-up of HR-HPV women treated with cryotherapy in a low-resource setting. *J Low Genit Tract Dis*. 18(4):333–7. doi:10.1097/LGT.0000000000000029 PMID:24977628

Stelzle D, Tanaka LF, Lee KK, Ibrahim Khalil A, Baussano I, Shah ASV, et al. (2021). Estimates of the global burden of cervical cancer associated with HIV. *Lancet Glob Health*. 9(2):e161–9. doi:10.1016/S2214-109X(20)30459-9 PMID:33212031

Strander B, Andersson-Ellström A, Milsom I, Sparén P (2007). Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population-based cohort study. [Erratum in: BMJ. 2008 377:a1186] *BMJ*. 335(7629):1077. doi:10.1136/bmj.39363.471806.BE PMID:17959735

Sultana F, Winch K, Saville M, Brotherton JML (2019). Is the positive predictive value of high-grade cytology in predicting high-grade cervical disease falling due to HPV vaccination? *Int J Cancer*. 144(12):2964–71. doi:10.1002/ijc.32050 PMID:30536935

Swift BE, Wang L, Jembere N, Kupets R (2020). Risk of recurrence after treatment for cervical intraepithelial neoplasia 3 and adenocarcinoma in situ of the cervix: recurrence of CIN 3 and AIS of cervix. *J Low Genit Tract Dis*. 24(3):252–8. doi:10.1097/LGT.0000000000000542 PMID:32384365

Tchounga B, Boni SP, Koffi JJ, Horo AG, Tanon A, Messou E, et al. (2019). Cervical cancer screening uptake and correlates among HIV-infected women: a cross-sectional survey in Côte d'Ivoire, West Africa. *BMJ Open*. 9(8):e029882. doi:10.1136/bmjopen-2019-029882 PMID:31473620

Teoh D, Musa F, Salani R, Huh W, Jimenez E (2020). Diagnosis and management of adenocarcinoma in situ: a Society of Gynecologic Oncology evidence-based review and recommendations. *Obstet Gynecol*.

135(4):869–78. doi:10.1097/AOG.0000000000003761 PMID:32168211

Thamsborg LH, Napolitano G, Larsen LG, Lynge E (2018). Impact of HPV vaccination on outcome of cervical cytology screening in Denmark – a register-based cohort study. *Int J Cancer*. 143(7):1662–70. doi:10.1002/ijc.31568 PMID:29707775

Thay S, Goldstein A, Goldstein LS, Govind V, Lim K, Seang C (2019). Prospective cohort study examining cervical cancer screening methods in HIV-positive and HIV-negative Cambodian women: a comparison of human papilloma virus testing, visualization with acetic acid and digital colposcopy. *BMJ Open*. 9(2):e026887.doi:10.1136/bmjopen-2018-026887PMID:30804036

Thida M, Thin KM, Thein ZM, Sein YY, Nyunt T, Sanda (2015). Effectiveness, safety and acceptability of the method of visual inspection with acetic acid (VIA) and cryotherapy based single-visit approach to cervical cancer prevention (CCP) in Kungyangon Township, Yangon Region, Myanmar. *Myanmar Medical Journal*. 57(3):48–56.

Tran PL, Kenfack B, Tincho Foguem E, Viviano M, Temogne L, Tebeu PM, et al. (2017). Efficacy of thermoablation in treating cervical precancerous lesions in a low-resource setting. *Int J Womens Health*. 9:879–86. doi:10.2147/IJWH.S142911 PMID:29238232

Trejo MJ, Lishimpi K, Kalima M, Mwaba CK, Banda L, Chuba A, et al. (2020). Effects of HIV status on non-metastatic cervical cancer progression among patients in Lusaka, Zambia. *Int J Gynecol Cancer*. 30(5):613–8. doi:10.1136/ijgc-2019-000987 PMID:32200353

UNAIDS (2020). Global HIV and AIDS statistics – 2019 fact sheet. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS. Available from: https://aidsinfo.unaids.org/.

US Preventive Services Task Force (2018). Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 320(7):674–86. doi:10.1001/jama.2018.10897 PMID:30140884

van Aardt MC, Dreyer G, Pienaar HF, Karlsen F, Hovland S, Richter KL, et al. (2015). Unique human papillomavirus-type distribution in South African women with invasive cervical cancer and the effect of human immunodeficiency virus infection. *Int J Gynecol Cancer*. 25(5):919–25. doi:10.1097/IGC.0000000000000422 PMID:25950128

Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. (2005). Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*. 6(5):271–8. doi:10.1016/S1470-2045(05)70101-7 PMID:15863374

Viviano M, DeBeaudrap P, Tebeu PM, Fouogue JT, Vassilakos P, Petignat P (2017). A review of screening strategies for cervical cancer in human immunodeficiency virus-positive women in sub-Saharan Africa. *Int J Womens Health*. 9:69–79. doi:10.2147/IJWH.S103868 PMID:28203108

von Karsa L, Arbyn M, De Vuyst H, Dillner J, Dillner L, Franceschi S, et al. (2015). European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. *Papillomavirus Res*. 1:22–31. doi:10.1016/j.pvr.2015.06.006

Wentzensen N, Arbyn M, Berkhof J, Bower M, Canfell K, Einstein M, et al. (2017). Eurogin 2016 Roadmap: how HPV knowledge is changing screening practice. *Int J Cancer*. 140(10):2192–200. doi:10.1002/ijc.30579 PMID:28006858

WHO (2011). WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/44776.

WHO (2014). Comprehensive cervical cancer control: a guide to essential practice. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/144785.

WHO (2015). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/186275.

WHO (2019). WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/329299.

WHO (2021). WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. 2nd ed. Geneva, Switzerland: World Health Organization. Available from: https://apps.who.int/iris/handle/10665/342365.

Womack SD, Chirenje ZM, Gaffikin L, Blumenthal PD, McGrath JA, Chipato T, et al. (2000). HPV-based cervical cancer screening in a population at high risk for HIV infection. *Int J Cancer*. 85(2):206–10. doi:10.1002/(SICI)1097-0215(20000115)85:2<206::AID-IJC10>3.0.CO;2-Q PMID:10629079

Zeferino LC, Bastos JB, do Vale DBAP, Zanine RM, de Melo YLMF, Primo WQSP, et al. (2018). Guidelines for HPV-DNA testing for cervical cancer screening in Brazil. *Rev Bras Ginecol Obstet*. 40(6):360–8. doi:10.1055/s-0038-1657754 PMID:29874685

Zhao XL, Liu ZH, Zhao S, Hu SY, Muwonge R, Duan XZ, et al. (2020). Efficacy of point-of-care thermal ablation among high-risk human papillomavirus positive women in China. *Int J Cancer*. 148(6):1419–27. doi:10.1002/ijc.33290 PMID:32895912

6. SUMMARY

6.1 Cervical cancer

6.1.1 Cervical cancer burden

Cervical cancer is the fourth most commonly diagnosed cancer type in women worldwide, with an estimated 604 000 new cases in 2020. It is also the fourth most common cause of cancer death in women, with an estimated 342 000 deaths in 2020. The burden of cervical cancer varies markedly across the world, with a 10-fold variation between the highest and lowest incidence rates and a more than 15-fold variation between the highest and lowest mortality rates. The incidence and mortality rates are highest in sub-Saharan Africa. The incidence rates are lowest in Western Asia and Australia and New Zealand, and the mortality rates are lowest in Australia and New Zealand and Western Europe. The highest cervical cancer incidence and mortality rates are generally observed in countries with the lowest levels of the Human Development Index. The incidence rates are also higher in countries that have a high prevalence of HIV infection and/or lack sustained cervical cancer screening programmes. Three patterns emerge from an analysis of trends in age-standardized incidence rates over time in different countries: (i) a decrease in rates over the years, (ii) an increase in overall rates, and (iii) an increase in rates in the younger age groups.

6.1.2 Cervical neoplasia

More than 90% of cases of cervical cancer are caused by persistent infection with 12 genetically related human papillomavirus (HPV) types in the alpha genus. HPV16 (in the alpha-9 species) causes about 60% of cases of squamous cell carcinoma, which comprises most of the global cervical cancer burden. HPV18 and HPV45 (in the alpha-7 species) cause 15% and 5% of cases of squamous cell carcinoma, respectively. Other closely related alpha-9 types (HPV31, HPV33, HPV35, HPV52, and HPV58) together account, with some regional variation, for 15% of cases of squamous cell carcinoma. The remaining carcinogenic types (HPV39 and HPV59 in alpha-7, HPV51 in alpha-5, and HPV56 in alpha-6) together cause about 5% of cases of squamous cell carcinoma. HPV-associated cases of adenocarcinoma are caused half by variants of HPV16 and half by HPV18 or HPV45 (and only uncommonly by other types, particularly in alpha-7).

The carcinogenicity of HPV is explained mainly by cell-cycle disruption and anti-apoptosis induced by the two major oncogenes, E6 and E7. HPV infections are very common and are usually benign. However, when they are persistent, infections with carcinogenic types may shift from the usual and common productive state (i.e. the complete life-cycle designed to produce

new virus particles). Instead, the virus can enter an abortive or transforming state characteristic of precancer, driven by interference of E6 and E7 with normal cell growth and differentiation. These changes underlie almost all cervical screening, triage, and diagnostic tests designed to detect precancer. The junction between the squamous lining of the vagina and ectocervix and the glandular lining of the endocervical canal (the squamocolumnar junction) is a ring of epithelium that is uniquely susceptible to HPV-induced carcinogenesis.

There is a well-established set of necessary intermediate states leading from normal cervical cells to invasive cancer. With a combination of microscopic and type-specific HPV test methods, the following states can be distinguished: normal cervix (uninfected), HPV infection (type-specific carcinogenic), precancer, and cancer. Precancers and cancers are subdivided into the predominant squamous pathway and the uncommon glandular pathway.

HPV infections act independently of each other, although they tend to be co-transmitted easily through direct sexual contact, leading to a peak of new infections in the decade after the age at the start of sexual activity. The odds of acquiring a given HPV infection are highly correlated with the prevalence of that type in the population. HPV16 is the most common carcinogenic type and poses the highest risk of precancer and invasive cancer. In the absence of progression to precancer, the average time to HPV clearance is similar for all HPV types. An individual woman may clear multiple types while a single causal type persists. Clearance is thought to relate mainly to cell-mediated immune control; in immunocompetent populations, most HPV infections of any type are no longer apparent within 1 year, and persistence past 2–3 years is uncommon (and is strongly linked with development of precancer). A population's prevalence of HPV infection in adult women is a critical determinant of cervical screening strategies. Women

living with HIV with impaired cellular immunity have a high HPV prevalence and require separate consideration.

Precancer can develop within a few years of HPV infection and peaks in the decade after the average age of onset of sexual activity (e.g. 25–35 years in many settings). In contrast, invasive cancer typically takes decades to develop, passing through a prolonged period of non-invasive growth around the circumference of the squamocolumnar junction.

The classification of cervical cancer follows the current World Health Organization (WHO) classification, which was revised in 2020. Most cervical cancers are HPV-associated carcinomas, but a small percentage of tumours are not associated with HPV infection. The most common cervical cancer types are squamous cell carcinoma and adenocarcinoma, which account for more than 95% of all cervical cancers. Most cervical squamous cell carcinomas (93–95%) and adenocarcinomas (75–90%) are HPV-associated. Both cancer types have precursor lesions. The terminology for squamous cell carcinoma precursors has changed over time, but the two approaches currently in widespread use are the cervical intraepithelial neoplasia (CIN) and squamous intraepithelial lesion (SIL) systems. For adenocarcinoma, precursor lesions are referred to as adenocarcinoma in situ.

Tumour staging assesses the extent of tumour spread and is the most important determinant of clinical management. The International Federation of Gynecology and Obstetrics (FIGO) staging system is most commonly used clinically, in conjunction with the tumour–node–metastasis (TNM) staging system to provide assessment particularly of lymph node metastasis, which has not traditionally been included in the FIGO system. The revised FIGO staging system published in 2018 added lymph node metastasis and pathological and radiological investigation to clinical assessment, and there is early evidence of improved patient stratification using

the 2018 system. In some countries, cervical cancer is diagnosed predominantly at an early stage (localized or FIGO stage I), but in others it is diagnosed at a more advanced stage (predominantly regional or FIGO stage II). In all countries, survival is strongly stage-dependent, with 5-year survival ranging from more than 90% for localized disease to less than 10% where distant disease is present.

Treatment options for precancer include excisional techniques, such as large loop excision of the transformation zone and cold-knife conization, and ablative techniques, such as cryotherapy and thermal coagulation. Squamous precancerous lesions can be treated with any of the above-mentioned techniques, whereas glandular precancer (adenocarcinoma in situ) is treated with excisional techniques. Treatment modalities for precancer have similar and high rates of success, although cryotherapy has varied outcomes compared with other treatment modalities. Recurrence of precancer after treatment may occur. Harms of treatment, primarily related to excisional techniques, include bleeding, infection, cervical stenosis, and premature delivery.

Treatment of invasive cervical cancer is based on the stage and size of the tumour. Surgical management is recommended for early cervical cancers, whereas advanced cervical cancers are treated with chemotherapy and radiation.

6.2 Cervical cancer screening programmes

The purpose of cervical cancer screening and treatment is to reduce the incidence of and mortality from cervical cancer by identifying women with precancerous cervical lesions and early invasive cancer and treating them appropriately. Adherence to and high quality of the entire screening and management pathway are central to the effectiveness of a screening programme; measures should be in place to ensure high coverage of the target population, high quality of the primary screening test, effective follow-up of women with positive screening test results, and appropriate subsequent treatment and care.

Various national and international guidelines on cervical cancer screening and treatment have been produced and/or updated, based on available resources and prevention approaches. Existing screening initiatives are not always reported properly, which hinders assessment of the availability of cervical cancer screening worldwide and prevents comparison between countries.

6.2.1 WHO African Region

Most countries in the WHO African Region have not implemented multistep cervical cancer screening with sufficient population coverage, because of meagre existing health-service infrastructure, a lack of human resources, and the low level of investment in health services. However, many countries in the region have implemented pilot or investigational screening programmes based on the screen-and-treat approach, using the visual inspection with acetic acid (VIA) test coupled with ablative procedures for precancerous lesions on the same day. These programmes are often integrated into the existing infrastructure dedicated to HIV care and reproductive health services.

6.2.2 WHO Eastern Mediterranean Region

In the WHO Eastern Mediterranean Region, most countries practise opportunistic screening based on cytology. Only Morocco, the Syrian Arab Republic, and Tunisia have implemented a screening programme within a national cancer control plan. In Morocco, VIA is the main test used in the public sector; in the other two countries, cytology is used. However, none of these three countries have an active invitation mechanism for screening; women are typically offered

cervical cancer screening when they visit a primary health-care unit or their gynaecologist. Therefore, participation rates remain low.

6.2.3 WHO European Region

In the European Union, the Council recommendations on cancer screening have contributed to the development of a common framework for the implementation of organized population-based cervical cancer screening programmes. European Union guidelines provide evidence-based recommendations for quality-assured screening programmes and key performance indicators. By July 2016, 22 European Union Member States had implemented, piloted, or planned population-based cervical cancer screening programmes. However, only nine of these countries had completed nationwide rollout. Outside the European Union, national organized population-based programmes have been implemented in Iceland, North Macedonia, Norway, and Turkey. In the countries of the former Soviet Union, cervical screening is mostly opportunistic, and those countries that have screening programmes lack widespread call–recall systems, have low coverage, and do not have quality assurance systems. Cytology remains the primary screening method in most countries in the European region, but HPV primary screening is being introduced in an increasing number of countries.

6.2.4 WHO Region of the Americas: North America

Canada and the USA have substantial differences with respect to the structure of their health systems and delivery of cervical cancer screening. Although cervical cancer screening is well established in Canada and the USA, an overlap of organized and opportunistic screening exists, particularly in the USA; in Canada, cervical cancer screening is provided mostly through organized programmes with invitation and reminder systems. In Canada, cytology remains the primary screening test, although some provinces are starting the transition to HPV primary screening. In the USA, guidelines recommend HPV testing either as a stand-alone test or as a co-test with cytology. There is high coverage in both countries.

6.2.5 WHO Region of the Americas: Latin America and the Caribbean

Up to 2019, all countries in the Latin American region and 12 out of 21 countries in the Caribbean had defined recommendations or policies for cervical cancer screening. Latin American countries have a long-standing tradition in cervical cancer screening, and most have updated their screening recommendations during the past decade. HPV testing is part of national recommendations in 13 countries in Latin America and the Caribbean, with self-sampling considered in four countries. Screen-and-treat approaches are recommended in eight Latin American and four Caribbean countries, and VIA is recommended as the screening test in most of them. Comprehensive programme reports are not available, and the coverage varies between countries.

6.2.6 WHO South-East Asia Region

In the countries in the WHO South-East Asia Region, organized population-based cervical cancer screening using cytology has been implemented in Bhutan, Sri Lanka, and Thailand, and Thailand introduced HPV-based testing in 2020. India, Indonesia, Myanmar, and Nepal have national guidelines for cervical cancer screening and policies using VIA; however, the screening coverage in these countries is low.

6.2.7 WHO Western Pacific Region

In the WHO Western Pacific Region, Hong Kong Special Administrative Region, New Zealand, the Republic of Korea, and Taiwan, China, have well-established population-based cervical screening programmes using cytology-based screening. HPV testing replaced conventional cytology for primary screening in Australia starting in 2017 and in Singapore in 2019. New Zealand is transitioning to HPV-based screening. China has a national cervical screening programme, but the coverage is low; cervical cancer screening is mostly opportunistic and varies between the different provinces. Japan and Malaysia have national cytology-based screening programmes; however, the coverage is low. Other countries in this region also have some recommendations and strategies in place, but there is little published information on the screening activities.

6.2.8 Quality assurance of screening programmes

Quality assurance measures the quality of service delivered and enables variability in service to be identified and adjustments to be made so that uniform care is provided to the participants in screening programmes. Screening programmes establish agreed-upon performance standards and desired targets to improve outcomes. Performance indicators (also known as quality measures) are measurable evaluations of the ability of a screening programme to deliver high-quality care. Health information systems provide support for the monitoring and evaluation of screening programmes; however, these demand additional resources and thus may be challenging to implement. WHO has provided global, core, and optional quality indicators, which many international programmes have adapted into local screening programmes. Indicators are generally organized into screening, screening test results, treatment, service delivery, facility and laboratory linkages, and HIV service integration.

6.3 Participation in screening for cervical cancer

Participation in screening for cervical cancer is influenced by socioeconomic structural determinants and by intermediate determinants that operate at both an individual level and a health system level. The main determinants of participation are socioeconomic status, ethnicity, health insurance status, and education level, as well as the differential access of women to structural resources, power, authority, and control (gender inequality). Broad contextual and policy factors mediate the process and can act as buffers that modify the effect of social inequalities on participation in screening. Intermediate factors include women's lack of knowledge and awareness of cervical cancer and screening, fatalistic beliefs about cervical cancer and negative previous experiences with screening services, fear of cancer, stigma and shame associated with gynaecological procedures, and lack of social and family support. Screening performed as part of an organized population-based programme tends to improve the access of socially disadvantaged women to screening and diagnosis services.

At the provider level, barriers to participation in cervical cancer screening include fee-paid services and screening performed by male health-care providers. Facilitators of screening include encouragement from health-care providers to get screened, health-care providers having the same sociocultural background as the women, and health institutions that are organized to meet women's needs. Other factors that positively influence participation are the use of communication strategies or tools between health-care providers and women, and navigation services.

Interventions such as invitation letters, telephone calls, or text messages, as well as various educational modalities, increased screening participation. With regard to strategies targeting health-care providers, evidence from high-income countries concluded that evaluating provider performance in offering and/or delivering screening and giving feedback increased screening participation. The effectiveness of provider incentives in increasing screening participation is unclear.

Programmes that offered HPV self-sampling kits to women, either through opt-out strategies or via the general practitioner's practice, along with outreach activities, increased screening participation compared with cytology-based strategies. Opt-in strategies in which women had to request the HPV self-sampling kit were not more effective than other ways of inviting women to cytology-based screening.

Strategies using HPV self-sampling were more effective in increasing participation compared with approaches using VIA or those offering clinician-collected HPV testing. HPV self-sampling offered through periodic community health campaigns had higher screening participation rates compared with HPV self-sampling offered at government health facilities.

6.4 Preventive and adverse effects of cervical cancer screening methods

6.4.1 Visual screening methods

(a) Technical description

Visual examination after the application of acetic acid or Lugol's iodine was developed because of the suboptimal performance of the screening methods used in high-income countries when used in low- and middle-income countries. After application of acetic acid or Lugol's iodine to the cervix, the test result is described as negative, positive, or suspicious for cancer. VIA positivity rates vary considerably, partly because of the intrinsic subjectivity of the method and partly because of variable participant characteristics. Visual examination only enables an assessment of the ectocervical epithelium, and is not appropriate for postmenopausal women or in younger women with a type 3 transformation zone. Visual inspection with Lugol's iodine has not been widely investigated as a primary screening test for cervical cancer, but it has been used as an adjunct to VIA and as an aid to precise treatment.

A quality assurance system, including training, supervision, evaluation of programme activities and long-term impact, and an effective information system, should be considered in any VIA-based screening programme. However, it is a challenge to ensure adequate training and quality assurance of naked-eye techniques in some settings.

(b) Beneficial effects of screening using VIA

VIA has been evaluated in cross-sectional studies in various settings in Africa, Asia, and Latin America for its sensitivity and specificity in detecting high-grade cervical precancerous lesions, compared with conventional cytology. The accuracy of VIA showed large heterogeneity: in meta-analyses, the pooled sensitivity to detect cervical intraepithelial neoplasia grade 2 or worse (CIN2+) lesions ranged from 48% to 83%, and the pooled specificity varied from 84% to 97%. The accuracy of VIA screening depends largely on provider training, menopausal status, and quality assurance. VIA performs poorly in perimenopausal and postmenopausal women, and its specificity may be lower in women living with HIV.

The effect of VIA screening in controlled settings on cervical cancer incidence and/or mortality compared with control populations receiving usual care (very low prevalence of screening) has been evaluated in three large

cluster-randomized trials in India. There was consistent reduction in cervical cancer mortality, ranging from a non-significant 14% reduction to a significant 35% reduction in the three trials, after a single round of screening in two studies (women aged 30–59 years in the Osmanabad District and Dindigul District studies) and after four rounds of biennial screening in one study (women aged 30–64 years in the Mumbai study). The reduction in mortality in the above-mentioned studies may have come from clinical stage shift and effective treatment of cervical cancer rather than from prevention of invasive cancer by detection and treatment of high-grade cervical precancerous lesions (CIN2, CIN3, and adenocarcinoma in situ). Given the low detection rate of such lesions, it is likely that the significant 31% reduction in cervical cancer mortality in the Mumbai study has come from a stage shift and effective treatment of early-stage invasive cervical cancers, whereas the significant 35% reduction in mortality observed in the Dindigul District study seems to be predominantly due to both detection and effective treatment of precancerous lesions and stage shift of invasive cancers. As a result of detection and treatment of cervical precancerous lesions, a significant 25% reduction in cervical cancer incidence was observed in the Dindigul District study. A smaller randomized controlled trial in South Africa showed a 37% reduction in CIN2+ lesions detected 6 months after a VIA screen-and-treat round compared with a control group.

To date, there is no evidence of reduction of cervical cancer incidence or mortality from routine population-based VIA screen-and-treat and conventional screening programmes implemented in some countries, including several in Africa and Asia.

(c)   Harms of VIA

Harms of VIA have not been systematically studied or reported widely, either in research settings or in programmatic settings. The lack of reported evidence on harms suggests that visual screening tests for cervical neoplasia are considered safe. Mainly, physical harms due to VIA include harms related to unnecessary procedures and treatment after false-positive screening test results. Psychological harms include anxiety, fear, and stress due to the procedure and to a positive result.

6.4.2 Cytological methods

(a)   Technical descriptions

Cervical cytology involves collecting exfoliated cells from the transformation zone and endocervical canal, because the precursors of cervical squamous cell cancers occur mainly in the transformation zone. For the microscopic examination of these cells, the collected material is applied to a glass slide for conventional cytology or placed into a vial for liquid-based cytology. Liquid-based cytology can reduce the proportion of unsatisfactory smears, and residual cellular material can be used for additional tests, including HPV testing and molecular biomarkers. Computer-assisted techniques for processing and reading of cytology samples have been adopted in some countries. Because of the high cost and the need for specific equipment, liquid-based cytology is difficult to introduce into resource-constrained settings. The Bethesda system was developed for reporting the results of cervical cytology using a unified terminology and has been used worldwide, but with variability in individual cytological categories. Because cytological examination depends on manual collection and microscopic evaluation is subjective, laboratory management and quality assurance systems are of pivotal importance in cervical cytology.

(b) Beneficial effects of screening using conventional cytology

There is a large body of observational evidence on the beneficial effects of screening using conventional cytology. The previous *IARC Handbook* on cervical cancer screening evaluated seven cohort studies and 20 case–control studies from multiple countries and concluded that cervical screening using conventional cytology can reduce the incidence of and mortality from cervical cancer. The present review identified five further cohort studies and 20 case–control studies, which continue to support the effectiveness of cytology screening in reducing cervical cancer incidence and mortality. The available studies are a mixture of population-based studies using administrative data sets, which avoid participation and recall biases, and studies based on recruitment invitations, which probably suffer from these biases but obtain detailed information to adjust for confounders. In the only randomized controlled trial to compare cytology screening with no screening, about 30 000 women in India participated in each of the cytology and control groups for a single round of screening. After 8 years of follow-up, the incidence of cervical cancer in the cytology group was higher than, although not statistically significantly different from, that in the control group (hazard ratio, 1.34; 95% confidence interval [CI], 0.99–1.82). Mortality from cervical cancer was lower, but not significantly lower, in the cytology group than in the control group (hazard ratio, 0.89; 95% CI, 0.62–1.27).

Two published meta-analyses were reviewed, with only one overlapping study. In 2007, the International Collaboration of Epidemiological Studies of Cervical Cancer published an analysis of almost 36 000 women from 12 observational studies to analyse risk factors for cervical cancer and included history of cytology screening. Cytology screening was associated with a reduced risk of cervical cancer for both squamous cell carcinoma (relative risk, 0.46; 95% CI, 0.42–0.50) and adenocarcinoma (relative risk, 0.68; 95% CI, 0.56–0.82). A 2013 systematic review undertook a meta-analysis of 12 studies with almost 4800 cases and 18 000 controls, and found lower odds of having undergone cytology screening in women with cervical cancer (odds ratio, 0.35; 95% CI, 0.30–0.41) but noted a large degree of heterogeneity.

National-level long-term ecological trend data from multiple countries also support the effectiveness of cytology-based cervical screening at a population level.

(c) Beneficial effects of screening using liquid-based cytology

Liquid-based cytology is based on the same sampling method, staining, and interpretation as conventional cytology; thus, both methods use the same process to identify precancerous lesions.

A large body of evidence shows similar accuracy of liquid-based cytology compared with conventional cytology. Several systematic reviews reported that when atypical squamous cells of undetermined significance (ASC-US) was used as the test threshold, the pooled sensitivity for detection of CIN2+ and for detection of CIN3+ was similar for conventional cytology and liquid-based cytology. However, in some reviews the pooled specificity was higher for conventional cytology than for liquid-based cytology. The eight large randomized controlled trials and several recent double-testing studies, mostly implemented in population-based programmes, reported similar or higher sensitivity, with similar or lower positive predictive value, for liquid-based cytology compared with conventional cytology. The proportion of unsatisfactory slides was consistently lower with liquid-based cytology compared with conventional cytology in all population-based studies.

Two observational studies and one randomized controlled trial reported a good correlation between baseline detection rate and subsequent incidence of CIN2, CIN3, and invasive cancers with liquid-based cytology.

(d) Cytology based on Romanowsky–Giemsa staining

The term "Romanowsky staining" refers to several techniques used to stain cytological specimens, in which the Romanowsky effect is used to differentiate the cell components, i.e. chromatin is stained in purple and nuclei show shadows, enabling characterization of their morphology. Staining techniques based on the Romanowsky effect are known by several names, such as Romanowsky–Giemsa and May–Grünwald–Giemsa, and are used for different purposes in modern cytology. Currently, the technique is still used for cervical cancer screening in some countries of the former Soviet Union.

Despite a very extensive bibliographical search (including literature in Russian and/or predating electronic databases), the Working Group did not identify any study comparing the accuracy or efficacy of Romanowsky–Giemsa staining with that of conventional cytology in cervical cancer screening. The few reports on screening performance suggest a high variability in the proportion of unsatisfactory slides and detection of cervical lesions, and low specificity. No observational studies showed effectiveness in reducing the incidence of or mortality from cervical cancer of screening programmes implemented in countries where Romanowsky–Giemsa staining is used. The few informative population-based studies showed no effect. There are many possible explanations for not observing an effect in such studies, other than the accuracy of cytology.

(e) Harms of cytological techniques

Physical harms associated with pelvic examination and collection of cervical cytology samples include pain and, less commonly, vaginal bleeding, discharge, urinary problems, or feeling sick. Psychological harms such as anxiety can be experienced: (i) when samples are collected, (ii) as a result of waiting time to receive the results, (iii) from unsatisfactory smears, (iv) from abnormal results, and (v) upon follow-up because of abnormal results.

6.4.3 HPV testing

(a) Technical descriptions

HPV tests can be classified by the following parameters: the nucleic acid targeted (DNA or messenger RNA [mRNA]), the amplification method (signal amplification or target amplification), the method of identification of amplicons, the viral genes targeted, the level of genotyping detail (none, limited, extended, or full), the output result (qualitative or quantitative), and the inclusion of internal controls. HPV tests that separately identify the most carcinogenic HPV genotypes may enable fine-tuned risk-based management of women who are positive for carcinogenic HPV types. HPV tests are typically performed on cervical specimens taken by a health-care worker but can also be applied to self-collected vaginal samples or urine.

Various HPV assays have been validated for cervical cancer screening. Regulatory requirements for HPV assays differ around the world. Criteria have been developed for evaluating new HPV DNA assays in comparison with standard comparator tests. New HPV DNA tests may be accepted for screening if non-inferior sensitivity and specificity for CIN2+ compared with a standard comparator test and sufficient intralaboratory and interlaboratory reproducibility can be demonstrated. New validation criteria are being developed that will expand the choice

of standard comparator tests, the validation of HPV tests other than DNA tests, and HPV testing on self-collected samples. Certain HPV tests require certified laboratories with trained staff and strict quality control, whereas others can be performed in field conditions or even as a point-of-care test. Availability, costs, logistic and regulatory aspects, throughput capacity, automation, user-friendliness, and the need for running water and electricity are important factors that influence the choice of an HPV screening test in a particular setting and situation.

(b) Comparison of HPV DNA testing versus cytology

The evidence comparing HPV DNA testing with cytology screening consists of 29 cross-sectional diagnostic studies, eight randomized controlled trials in routine cervical screening and one randomized trial in a previously unscreened population, 10 population-based studies using results from regional, national, and pilot HPV DNA screening programmes, six co-testing cohorts, and one pooled analysis of seven other co-testing cohorts. In a pooled analysis of the 29 diagnostic studies with paired HPV DNA and cytology test results, HPV DNA testing was 37% more sensitive than cytology at detecting CIN3+ and 35% more sensitive at detecting CIN2+, at the expense of 6% lower specificity. In seven of the eight randomized controlled trials in routine screening, HPV-based screening by HPV DNA alone or co-testing detected significantly more CIN2+ than cytology in the first screening round. Six randomized controlled trials performed two rounds of screening. In five of them, HPV-based screening detected significantly fewer CIN2+ than cytology in the second screening round, and in four of them, only a minimal change in cumulative detection of CIN2+ over two rounds was observed, reflecting no increase in overdiagnosis.

A pooled analysis of four randomized trials in routine screening, with a median follow-up of 6.5 years, yielded a 40% lower cumulative

risk of cervical cancer in the HPV DNA-based screening arm compared with the cytology-based screening arm. In the randomized trial in a previously unscreened population, the cumulative cervical cancer mortality was 41% lower in the HPV-based screening arm than in the cytology-based screening arm after a follow-up of 8 years.

In eight of the 10 population-based HPV DNA screening studies, HPV-based screening detected significantly more CIN2+ than previous cytology screening. These studies also reported an increase in the proportion of positive HPV test results and colposcopy referrals, but the effect of HPV DNA screening on the proportion of CIN3+ detected in women referred for colposcopy was inconsistent across studies. Randomized controlled trials and co-testing cohorts reported a substantially lower 3–10-year risk of CIN3+ and an up to 70% lower risk of cancer after a negative HPV DNA test result than after negative cytology, which supports the use of longer intervals in HPV-based screening programmes.

(c) Comparison of HPV DNA testing versus VIA

Eight reviews and meta-analyses or pooled analyses, two randomized controlled trials, six cross-sectional studies, and a pooled analysis of two cohorts contributed to the comparison of HPV DNA testing and VIA on test accuracy, detection rate of high-grade cervical lesions, and cervical cancer incidence and mortality. The test accuracy of VIA was very heterogeneous across studies and prone to potential outcome misclassification. Overall, HPV DNA demonstrated higher pooled sensitivity than VIA, with a difference that was most pronounced in post-menopausal women.

A randomized controlled trial in South Africa showed a greater reduction in CIN2+ at 6 months after HPV DNA test-and-treat (77%) than after VIA-and-treat (37%) compared with no treatment, and a randomized controlled trial

in Osmanabad District, India, showed that, after 8 years of follow-up, greater reductions in the cumulative incidence of stage II or higher cervical cancer (> 2 times) and in cervical cancer mortality (> 1.6 times) were reached after a single round of screening with HPV DNA testing compared with VIA. For HPV DNA testing compared with VIA, the different studies did not consistently report a higher or lower proportion of colposcopy referrals or a larger number of colposcopies needed to detect one CIN2+ or CIN3+.

(d) Comparison of HPV DNA testing alone versus co-testing

HPV DNA testing alone versus co-testing (combined HPV DNA testing and cytology) has been evaluated in a meta-analysis, a joint analysis of cohort studies, four randomized controlled trials, seven prospective cohort studies, and retrospective analyses of a large laboratory database. The studies span nearly 15 years and differ in referral strategies, follow-up time, and outcomes examined (CIN2+, CIN3+, and invasive cancer). No evidence was found for the comparison of testing modalities regarding the outcome of mortality. Co-testing results in about 5% higher sensitivity but lower specificity than HPV DNA testing alone for outcomes of CIN2+ and CIN3+. The loss in specificity and the reduced positive predictive value of co-testing may lead to increased harms (namely, overdiagnosis of regressive lesions). Over longer follow-up, cumulative risks of CIN2+ and CIN3+ differ minimally between co-test-negative women and HPV-negative women.

(e) HPV testing on self-collected versus clinician-collected samples

Data on the comparison between self-collected vaginal samples and clinician-collected cervical samples are abundant for HPV DNA tests, with a key meta-analysis including 56 diagnostic test accuracy studies. In addition, three new accuracy studies and one study evaluating the longitudinal performance of HPV self-sampling were reviewed. The studies originate from all world regions except Oceania. The studies reviewed included different HPV DNA assays, all clinically validated, and different sampling devices and storage medium.

Similar sensitivity and specificity for the detection of CIN2+ or CIN3+ were observed when using polymerase chain reaction (PCR)-based HPV DNA tests on self-collected samples. Use of other types of HPV DNA assays for the detection of CIN2+, such as signal amplification, resulted in an average decrease of 15% in sensitivity and 4% in specificity. There was no indication that accuracy estimates for the detection of CIN2+ or CIN3+ were modified by sampling device or storage medium. Data on the long-term comparability were scanty.

The evidence for the detection of CIN2+ on specimens collected by self-sampling for HPV RNA tests based on three studies pointed to lower sensitivity and similar specificity compared with clinician-collected cervical samples.

Preliminary data on the introduction of self-sampling in nationwide programmes support its feasibility and effectiveness.

(f) Comparison of HPV RNA testing versus HPV DNA testing

Data on the accuracy of HPV RNA tests for the detection of CIN2+ were available for 11 studies on screening populations, four studies that reported on longitudinal outcomes, and 20 studies with triage of screen-positive cases, including one randomized trial. The studies were mainly from Europe, North America, and China.

Data on cross-sectional performance of RNA-based assays were consistent with higher specificity for CIN2+ compared with HPV DNA tests. This was achieved at the cost of a slight decrease in the sensitivity to detect CIN2+. Data on the accuracy to detect precancerous lesions in a primary screening setting with a follow-up of more than 4 years remain limited.

(g) Triage of women with a positive primary HPV screening test result

Appropriate triage testing, management, and follow-up of HPV-positive women is of critical importance to optimize the balance of benefits and harms of primary HPV screening. The general principle is to refer for diagnostic workup women who are at a higher risk of having a current or incipient precancer, to return to routine screening women who are at low risk, and to keep under surveillance women who are at intermediate risk. From a meta-analysis on the accuracy of tests used to triage HPV-positive women for detection of cervical precancer, including 93 studies, six commonly considered triage strategies were selected for assessment: (i) cytology at a threshold of ASC-US+, (ii) genotyping for HPV16/18; (iii) p16/Ki-67 immunocytochemistry (dual staining), (iv) VIA, (v) combined testing with HPV16/18 genotyping and cytology at a threshold of ASC-US+ (in which HPV16/18-positive women are referred directly for colposcopy and women who are positive only for other carcinogenic HPV types are further triaged with cytology), and (vi) combined testing with HPV16/18 genotyping and VIA (similar to strategy (v) but using VIA to triage women who are positive only for other carcinogenic HPV types). In the first four (single-test) strategies, p16/Ki-67 dual staining was more sensitive for detection of underlying CIN3+ (85%), with an associated specificity for < CIN2 of 69%. The combinations of HPV16/18 genotyping and another triage test (cytology at a threshold of ASC-US+ or VIA) reached a similarly high level of sensitivity for CIN2+ and CIN3+ as dual staining. However, the cross-sectional specificity of these combinations for CIN2+ was lower (< 60% for < CIN2).

More complex algorithms than those assessed here can be considered to fine-tune management, particularly in relation to the management of an intermediate-risk group who are positive for carcinogenic HPV but have a negative triage test result at the index test, for whom surveillance is an option. The acceptability of any triage approach is ultimately context-specific and depends on a range of factors, including the underlying risk of CIN3+ and invasive cervical cancer in a population, the available technological options for triage testing, the cost–effectiveness, and the acceptability of the testing process to women.

(h) Harms of HPV testing

Psychosocial harms in screening have been measured by administering questionnaires in screening cohorts and through qualitative research. A positive HPV test result is associated with increased levels of anxiety and distress, but these levels decrease over time. A positive HPV test result may also cause concerns about cancer and evoke feelings of stigma and shame. The psychosocial impact of HPV testing depends on cultural factors and communication strategies and varies across health systems. A web-based survey and interview and questionnaire studies indicated that anxiety can be reduced by communicating that HPV infection is common. Two randomized controlled trials in European countries studied the psychosocial impact of HPV-based screening compared with cytology-based screening. These trials reported similar average levels of anxiety and distress in the two arms, but one of them reported a reduced level of sexual satisfaction in the HPV-based screening arm. The cervical sampling procedure also causes psychological and physical harms, which may be reduced by offering the option of self-collected vaginal sampling for HPV testing. Two meta-analyses together with recent studies of self-sampling showed that self-sampling lowers anxiety, discomfort, and pain and is less embarrassing than sampling by a clinician. Most women in these studies expressed a preference for self-sampling as a future sampling method, but some women were worried about the accuracy of the HPV self-sampling test and their capacity to collect the sample correctly.

6.4.4 Colposcopy

A colposcope is a low-magnification, stereoscopic, binocular field microscope with a powerful light source. It is used for visual examination of the lower genital tract, including the cervix, vagina, and vulva. Colposcopy is the cornerstone of management of screen-positive or symptomatic women. It facilitates the identification of the transformation zone and the characterization and localization of intraepithelial lesions to guide biopsies, where necessary.

Different classifications have been used to describe colposcopic findings. Expertise in performing colposcopy is attained and maintained by comprehensive training, experience with an adequate caseload, and continuing professional development. However, colposcopy training and assessment is neither uniform nor quality-assured worldwide.

In a cytology-based screening, colposcopy shows high sensitivity and low specificity for the diagnosis of high-grade squamous intraepithelial lesion (HSIL)/CIN2+ when used at a threshold of "any colposcopic abnormality" (biopsy taken after suspicion of SIL/CIN of any grade); at a threshold of "high-grade colposcopic impression" (biopsy taken after suspicion of HSIL), colposcopy shows medium sensitivity but high specificity for HSIL/CIN2+. In HPV-based screening, the central diagnostic role of colposcopy is maintained but the clinical characteristics of the patients and the number of women referred for colposcopy are profoundly different.

Recently, it has been suggested that the risk of underlying histological HSIL can be estimated before colposcopic evaluation by combining the screening test results (cytology and/or molecular test results such as HPV testing and genotyping). In this strategy, the practice of colposcopy and biopsy can be modified depending on the risk of precancer. Moreover, information provided by the colposcopic impression is taken into account to guide the number of biopsies needed.

6.4.5 Emerging technologies

(a) Emerging visual and cytological technologies

Established guidelines for diagnostic research (the Standards for Reporting of Diagnostic Accuracy Studies [STARD] statement) have been adapted for technology development for cervical cancer screening. The process from discovery and development to clinical implementation is complex and involves multiple stakeholders. As the understanding of the natural history of cervical cancer has improved and technology development has accelerated, the timeline from discovery to clinical practice has become much shorter. The most important criterion for a new test or tool is whether the test result will improve clinical management. Two promising emerging technologies are the use of artificial intelligence-based image recognition to improve visual evaluation of the cervix and cytological interpretation.

As image-capture technology, Internet bandwidth, electronic storage capacity, and computing power have improved exponentially, it has become possible to develop complex systems for image capture, recognition, and interpretation. Using large annotated image banks, these systems use either the Internet cloud or small, powerful, cloud-independent computer devices to store and interpret the incoming images. A variety of approaches have been used to both screen and triage women by examining the cervix in the VIA or colposcopy setting. Most commonly, these systems discriminate between normal or low-grade squamous intraepithelial lesion (LSIL) and HSIL. No convincing real-life studies of sufficient power have been undertaken so far.

Early results from automated cytology systems have shown potentially valuable results for both morphological interpretation and quantitative assessment of p16/Ki-67 dual-stained slides. Some studies reported improved sensitivity and

specificity compared with manual evaluation of morphology and dual-stain assessment. This has the capacity to reduce unnecessary referral for colposcopy.

(b)   Emerging molecular technologies

DNA methylation of some human genes and coding regions of the HPV viral genome is associated with CIN and cervical cancer. Methylation patterns are different in CIN2+ compared with normal cervical tissue or moderate cervical lesions, and an increase in methylation is associated with severity. DNA methylation assays show promise for the detection of CIN2+ in triage of HPV-positive women, because they enable automation and self-sampling. Compared with cytology, molecular testing of DNA methylation is objective and decreases the risk of interpretation errors. Methylation of the following human genes has often been reported as providing promising biomarkers: *CADM1*, *EPB41L3*, *FAM19A4*, *MAL*, *miR-124-2*, *PAX-1*, and *SOX-1*; however, none of these biomarkers alone can detect cervical cancer. Increasing methylation is also observed in the E2, L1, and L2 viral coding regions as characteristic patterns, especially for HPV types 16, 18, 31, 33, and 45. A combined multi-type methylation assay might be preferable for triage of HPV-positive women.

A detection assay for the E6 oncoprotein from HPV16/18/45 has shown promising test performance when assessed as a primary screening method for cervical cancer or as a triage test for HPV-positive women in both clinician-collected and self-collected samples.

6.5   Screen-and-treat approach and women at differential risk

6.5.1   Screen-and-treat approach

Multistep cervical cancer screening programmes involving colposcopy and histology require considerable investment in infrastructure, training of a skilled workforce, and quality control efforts. Furthermore, multistep cervical cancer screening strategies require multiple visits with patient–provider interactions and have a substantial risk of loss to follow-up, particularly in resource-constrained settings. Screen-and-treat approaches are designed to require fewer resources compared with multistep programmes, and to decrease the need for repeat visits. Although different screen-and-treat strategies exist, the unifying feature is that treatment is performed without a colposcopy-directed biopsy and histological confirmation of precancer.

Current screening modalities used in screen-and-treat programmes include VIA and HPV testing. Although VIA is simple and widely available, it is also highly subjective and its performance is inconsistent. Point-of-care HPV testing can provide a similar turnaround time to that of VIA, with substantially improved accuracy. Typically, in screen-and-treat programmes more women need to undergo treatment than in multistep screening programmes; this increases the risk of overtreatment. Because of the high prevalence of HPV infections and CIN2+ lesions in women living with HIV, VIA may lead to additional overtreatment compared with HIV-negative women.

Treatment approaches include ablative treatment, such as cryotherapy and thermal ablation, and excisional treatment. Only a subset of women are eligible for ablative treatment, and therefore colposcopy and excisional treatment capacity is required in all programmes. Few studies have assessed the feasibility of full screen-and-treat programmes. A large randomized

trial in South Africa demonstrated a greater reduction in the prevalence of precancer with an HPV screen-and-treat protocol than with a VIA screen-and-treat protocol, compared with delayed evaluation. Novel approaches for screen-and-treat programmes or screen–triage–treat programmes that are undergoing evaluation include self-sampling with partial HPV geno-typing, and automated visual evaluation.

6.5.2 Screening of women at differential risk

(a) Screening of women living with HIV

The burden of cervical cancer remains significantly higher in women living with HIV than in HIV-negative women. Incidence rates vary widely by world region and are highest in eastern and southern Africa. Systematic reviews and meta-analyses have reported that women living with HIV have a 2–5-fold higher incidence of HSIL and a 4-fold higher risk of invasive cervical cancer compared with HIV-negative women. HIV infection can cause rapid progression from HPV infection to cancer.

A recent systematic review and meta-analysis reported that women living with HIV taking antiretroviral therapy had a lower prevalence of carcinogenic HPV infections, a lower incidence of HSIL, and a lower incidence of invasive cervical cancer compared with those not taking antiretroviral therapy. The greatest reductions were observed in women with sustained HIV viral suppression and in women initiating anti-retroviral therapy at a high CD4+ cell count.

The screening tests for precancerous lesions in women living with HIV are the same as in HIV-negative women, but the performance is affected by the high prevalence of HPV infection. Treatment of HSIL in women living with HIV can be ablative or excisional, and several studies have observed a higher risk of recurrence after treatment in women living with HIV than in HIV-negative women.

(b) Screening of older women

After menopause, there are marked physio-logical changes of the cervix, which can some-times result in discomfort during speculum insertion, unsatisfactory specimen collection, lower-accuracy results, and potential harm from overtreatment. Therefore, it is imperative to determine the balance of benefits and harms of cervical cancer screening in older women.

In well-screened populations, most published national guidelines are based on the natural history of HPV infections, surveillance trends, expert opinion, and modelling; most guidelines recommend stopping screening at age 65 years in women with prior adequate negative screening history. However, empirical data are scant on when to stop screening in women aged 65 years and older, in previously unscreened women, in women with an inadequate screening history, and in women with continuing risk factors for the development of cervical cancer, such as women living with HIV.

Both cytology and primary HPV testing can be used to screen postmenopausal women to identify test-positive cases that require treatment with effective available modalities. In most guide-lines, primary HPV testing every 5 years is the preferred method of screening in older women, and as data accumulate this interval may be lengthened to 7 years. Several published studies have reported that the protection offered by a negative cytology test result at age 60–65 years is not lifelong, so extending screening beyond age 65 years will offer longer protection against cervical cancer even in well-screened popula-tions, with potential harms of treating women with false-positive results at colposcopy.

(c) Screening of women with a personal history of precancerous lesions

Women who have been treated for known or suspected HSIL/CIN2+ or adenocarcinoma in situ are at higher risk of subsequent disease.

Although most women who have undergone treatment for precancerous cervical lesions do not experience a recurrence of disease, they should undergo post-treatment management and surveillance for test of cure before returning to routine screening. Most current guidelines are based on the pre-treatment diagnosis and the post-treatment histology, including the margin status. Initial testing protocols include cytology and/or HPV-based testing, with a range of surveillance intervals (i.e. 6 months or 12 months) for 1–5 years; some guidelines lengthen surveillance intervals after successive normal test results to support test of cure. After accumulating a history of normal test results, women may return to routine screening intervals or may continue with a less-intensive surveillance protocol. The most recent guidelines emphasize follow-up with HPV-based testing to determine test of cure and return to routine screening. Newer risk-based surveillance protocols take into account current screening test results and previous screening test results and biopsy results.

(d)   Screening of HPV vaccinated populations

In late 2006, HPV vaccination became a primary prevention front in cervical cancer control, complementing screening, a secondary prevention activity. In 2018, WHO established as a priority the elimination of cervical cancer as a public health problem, based on the proven effectiveness of both strategies and the expectation of their joint impact in reducing the incidence of cervical cancer to below the target of 4 new cases per 100 000 women per year.

Although vaccination and screening are complementary, they are managed very differently because they apply to different periods in a woman's lifetime and are managed by different parts of the health-care system. However, they can both be viewed as preventive steps in the same continuum in the natural history of cervical cancer. Vaccination prevents the acquisition of HPV infection, the intermediate precursor to precancer development.

As successive birth cohorts of vaccinated women reach the age of screening, the prevalence of precancer decreases, and as a result the efficiency of screening falls via a gradual decrease in the positive predictive value of screening. Although this effect happens with any screening technology, it is expected that cytology will be more severely affected. Because of its performance characteristics, reproducibility, and reliance on objective criteria for defining positivity, primary HPV testing is a more rational approach to the screening of women after vaccination. However, even with the adoption of HPV testing, questions arise regarding the benefits and potential harms of maintaining the same screening frequency in vaccinated and unvaccinated women. A related question is whether populations with high vaccination coverage should adopt less-intensive screening by starting screening later in life and being screened less frequently.

Many jurisdictions and professional bodies have considered the appropriateness of screening policies based on vaccination history. To date, only Italy has proposed screening algorithms that depend on vaccination status and lesion prevalence; all other proposals specify screening policies irrespective of HPV vaccination status.

The integration of vaccination and screening as public health processes that share information, data, resources, and expertise can provide a unified surveillance mechanism to monitor the long-term impact of both prevention fronts and provide an empirical basis for future changes in screening policies.

7. EVALUATIONS AND COMPARISON STATEMENTS

7.1 Visual inspection with acetic acid

Visual inspection with acetic acid (VIA) *is established to reduce mortality from cervical cancer* **(Group A).**

Visual inspection with acetic acid (VIA) *may reduce the incidence of cervical cancer* **(Group B).**

The evidence for a reduction in cervical cancer mortality after VIA screening comes from consistent and significant reduction in cervical cancer mortality after a single round (in the Dindigul District and Osmanabad District studies) or multiple rounds (in the Mumbai study) of VIA screening documented in three population-based cluster-randomized intervention trials. The significant reduction in cervical cancer mortality in the Mumbai study has come from clinical stage shift and effective treatment of early-stage invasive cervical cancers as suggested by the low detection rate of high-grade cervical intraepithelial neoplasia (CIN) despite four rounds of biennial screening, whereas both early detection and effective treatment of high-grade cervical precancerous lesions and stage shift of invasive cancers contributed to the significant reduction in cervical cancer mortality in the Dindigul District study and the non-significant reduction in cervical cancer mortality in the Osmanabad District study.

Reduction in cervical cancer incidence after VIA screening has been demonstrated in one of the three cluster-randomized trials (the Dindigul District study). About 44% of screen-positive women in the Dindigul District study received treatment for CIN (including CIN1, CIN2, and CIN3) lesions. The high frequency of treatment of screen-positive women with lesions might have led to the significant reduction in cervical cancer incidence in the Dindigul District study.

Screening regimen to which the evaluation applies. This evaluation applies to VIA screening provided by well-trained health-care workers and implemented with quality assurance and with appropriate follow-up and treatment. VIA is not indicated in women younger than 30 years or in postmenopausal women, and caution is needed in perimenopausal women and in women living with HIV.

Whether effectiveness has been established. Effectiveness to reduce cervical cancer incidence and mortality has not been documented in population-based screening programmes.

Magnitude of benefits and harms. The benefits in terms of reduction in cervical cancer incidence and mortality vary depending on the expertise and experience of the test providers, the adherence to treatment of lesions, the efficiency of the overall programme, and the characteristics (e.g. age, menopausal status) and risk of the underlying target population. A high

frequency of false-positive VIA tests is likely to increase the relative proportion of harms after VIA screening.

Balance of benefits and harms. The benefits may outweigh the harms, but only in VIA screening programmes implemented by well-trained providers, with quality assurance and with appropriate treatment of lesions and follow-up care.

Additional considerations. The harmful effects of VIA have not been systematically studied in visual screening studies or reported widely, either in research settings or in programmatic settings. Visual screening tests for cervical neoplasia are considered safe because few women report adverse events after VIA; however, the current lack of systematically collected and reported data should be addressed, and this should be an essential part of quality improvement activities where VIA is in use.

It is too early to consider the safety of new visual screening techniques such as visual inspection using digital cameras and automated visual evaluation of cervical images from contemporary digital cameras, because of a lack of data.

The main inherent risk of VIA remains its inability to precisely and reliably recognize endocervical disease, which means that it may falsely reassure women when no lesion is detected; this may eventually result in a screening programme being discredited.

Because of the high prevalence of human papillomavirus (HPV) infection and CIN grade 2 or worse (CIN2+) lesions in women living with HIV, VIA may lead to additional overtreatment compared with HIV-negative women.

VIA is not recommended for postmenopausal women, although ageing populations are becoming a major challenge for health-care services in many countries.

VIA has been implemented in resource-constrained settings or countries with low access to health care, because of its low cost, the low infrastructure requirements, and the possibilities

to reduce losses to follow-up in screen-and-treat approaches. A wide range of health-care workers provided VIA in studies and continuing programmes, but proper training is needed and harmonized interpretation criteria for positivity still need to be defined.

7.2 Conventional cytology

Conventional cervical cytology *is established to reduce the incidence of cervical cancer* and *to reduce mortality from cervical cancer* **(Group A).**

The evidence for a reduction in cervical cancer incidence and mortality after conventional cervical cytology screening comes from studies comparing cervical cancer incidence and mortality rates in women who were screened with those in women who were not screened, and from declining cervical cancer incidence and mortality rates from population-based registries in multiple countries and world regions.

Screening regimen to which the evaluation applies. The evaluation applies to conventional cervical cytology screening (Papanicolaou testing) performed within a quality-assured laboratory system with appropriate follow-up and treatment, recognizing the subjective nature of the test and the strong need for appropriate training and systems to ensure and maintain accuracy.

Whether effectiveness has been established. Conventional cervical cytology has been established to be effective in reducing cervical cancer incidence and mortality in population-based programmes.

Magnitude of benefits and harms. The benefits in terms of absolute reduction in cervical cancer incidence and mortality vary depending on the underlying population risk and the efficiency of the screening programme. Psychological benefits include a sense of reassurance after a negative test result. Psychological harms include anxiety related to the screening

procedure, receipt of results, and subsequent diagnostic and treatment pathways. A need to repeat the sample collection because of unsatisfactory specimens may be more frequent than with other methods of cervical screening. Physical harms of conventional cytology may include pain and discomfort during the screening procedure. The potential harms of any subsequent diagnostic procedures or treatment, such as risks of bleeding, infection, or adverse obstetric outcomes, are shared with other cervical screening methods.

Balance of benefits and harms. The benefits generally outweigh the harms. There is less certainty for women younger than 30 years, in whom effectiveness is less well demonstrated and the potential for obstetric harms is greater. Although studies demonstrate continuing effectiveness after age 65 years, the potential benefit in women with a history of regular normal screens may be small, and the physical discomfort associated with screening is likely to increase with age.

Additional considerations. The evidence supports significant benefits from well-organized programmes. The evidence suggests that protection from a single screen wanes over time, that consistent, regular screening lowers the risk more substantially than ad hoc or single-time screening does, that the risk of squamous cell carcinomas of the cervix is reduced by a greater magnitude than that of other cervical cancers, that screening of women younger than 30 years has less consistent evidence of effectiveness, and that screening of older women (e.g. older than 65 years) continues to be effective, with potentially greater benefits in those without a history of regular normal screens.

7.3 Liquid-based cytology

Liquid-based cytology *is established to reduce the incidence of cervical cancer* and *to reduce mortality from cervical cancer* (Group A).

The evidence for a reduction in cervical cancer incidence and mortality after liquid-based cytology screening comes from randomized controlled trials and population-based nationwide observational studies comparing the accuracy, efficacy, and effectiveness of liquid-based cytology with those of conventional cytology, and considering that the techniques are sufficiently similar. A large body of evidence shows similar accuracy and effectiveness of liquid-based cytology compared with conventional cytology.

Screening regimen to which the evaluation applies. The efficacy has been tested in programmes adopting cytology as a stand-alone first-level test, with different strategies of referral for colposcopy, including repeating cytology for atypical squamous cells of undetermined significance (ASC-US) and low-grade lesions, HPV triage for ASC-US, and direct referral for colposcopy of all cytological abnormalities.

Whether effectiveness has been established. Liquid-based cytology proved to be as effective as conventional cytology in reducing cervical cancer incidence in nationwide population-based programmes. Despite some issues in implementation, liquid-based cytology had small or no negative impacts on screening programme performance.

Magnitude of benefits and harms. The benefits and harms of liquid-based cytology have been measured only in comparison with those of conventional cytology. The benefits in terms of reduction in cervical cancer incidence were shown to be very similar to those of conventional cytology. The reduction in the proportion of unsatisfactory specimens decreases the need to repeat the sample collection, which is associated with anxiety for women and resource

consumption. However, some studies of liquid-based cytology showed increased sensitivity for low-grade lesions, which results in a higher referral rate for further assessment.

Balance of benefits and harms. The benefits of screening with liquid-based cytology outweigh the harms.

Additional considerations. In high-income countries, the introduction of liquid-based cytology into screening programmes has been driven mostly by the lower proportion of unsatisfactory specimens and by the opportunity to perform both molecular and cytology tests, in particular HPV tests, with a single sample. This opportunity has facilitated these two-step strategies, both when HPV testing is used as a triage test for ASC-US or low-grade squamous intraepithelial lesion (LSIL) cytology and when cytology is used to triage HPV-positive women. Some programmes have considered these advantages to overcome the barrier of higher costs.

7.4 HPV nucleic acid testing

HPV nucleic acid testing *is established to reduce the incidence of cervical cancer* and *to reduce mortality from cervical cancer* **(Group A).**

The evidence for a reduction in cervical cancer incidence and mortality after screening with HPV nucleic acid testing comes from one randomized controlled trial showing that HPV testing reduces cervical cancer mortality, a pooled analysis of four randomized controlled trials showing that HPV testing leads to a greater reduction in cervical cancer incidence than cytology does, and screening cohorts and diagnostic studies comparing HPV testing with cytology and/or VIA.

Screening regimen to which the evaluation applies. The evaluation applies to HPV DNA testing and HPV messenger RNA (mRNA) testing.

Magnitude of benefits and harms. The bulk of the evidence is from studies of HPV DNA testing. HPV mRNA testing has been shown to have accuracy levels similar to those of HPV DNA testing for detection of CIN2+, and a negative HPV mRNA test has a lower 3-year risk of CIN2+ than negative cytology does. The first round of HPV testing, followed by triage testing of HPV-positive women, in regional, national, and pilot HPV screening programmes confirmed that HPV screening detects more precancerous lesions than cytology screening does. HPV screening also increased the proportion of positive screening results and colposcopy referrals and had an inconsistent effect on the proportion of CIN3+ in women referred for colposcopy (the positive predictive value for CIN3+). A positive HPV test result is associated with increased levels of anxiety and distress and may cause concerns about cancer and feelings of stigma and shame.

Balance of benefits and harms. The benefits outweigh the harms for women aged 30 years and older. There is less certainty for women younger than 30 years, especially when triage testing of HPV-positive women is not in place. The benefits–harms profile can be further improved by extending screening intervals to at least 5 years, because longitudinal HPV screening studies have shown very low risks of CIN3+ and cancer after a negative HPV DNA test.

Additional considerations. Testing should be performed with clinically validated tests. HPV testing can also be performed on a self-collected vaginal sample. Diagnostic studies have shown that similar accuracy for detection of CIN2+ can be achieved with HPV DNA testing on a self-collected sample and a provider-collected sample. On average, self-collection is better tolerated, both physically and psychologically, than provider-collected sampling.

7.5 Cytology based on Romanowsky–Giemsa staining

Cytology based on Romanowsky–Giemsa staining *is not classifiable as to its capacity to reduce the incidence of cervical cancer or to reduce mortality from cervical cancer* (Group C).

The literature search performed, which included a manual search for publications dating from before electronic literature databases, did not retrieve any comparative study on the accuracy, efficacy, or effectiveness of cytology based on Romanowsky–Giemsa staining in cervical cancer screening. Data on the performance of Romanowsky–Giemsa staining in screening programmes suggest low reproducibility and low specificity. The technique is adopted mainly for historical reasons and because of the lower costs of a single examination and the wider availability of materials compared with the Pap test. However, the high rate of unsatisfactory stains and the low specificity imply high induced costs for repeated tests. The absence of an international community for standardization of interpretation criteria makes quality improvement difficult.

7.6 HPV DNA testing versus VIA

HPV DNA testing has been compared with VIA in eight reviews and meta-analyses, two randomized controlled trials, six cross-sectional studies, and a pooled analysis of two cohorts.

Benefits. HPV DNA testing leads to a greater reduction in the incidence of stage II or higher cervical cancer and in cervical cancer mortality than VIA does. HPV DNA testing also detects more high-grade cervical lesions than VIA does.

Harms. Because of the high variability of VIA, the effect on rates of referral for colposcopy was inconsistent across studies. Therefore, the harms cannot be compared.

Balance of benefits and harms. Compared with VIA, HPV DNA testing shows higher benefits, which outweigh the potential increase in the rates of referral for colposcopy. VIA has substantial other limitations, such as subjectivity, heterogeneity, and potential outcome misclassification.

7.7 HPV DNA testing versus cytology

HPV DNA testing has been compared with cytology in 29 diagnostic studies, eight randomized controlled trials in routine cervical screening and one randomized controlled trial in a previously unscreened population, 10 population-based studies using results from regional, national, and pilot primary HPV screening programmes, six co-testing cohorts, and one pooled analysis of seven other co-testing cohorts.

Benefits. HPV DNA testing leads to a greater reduction in cervical cancer incidence and mortality than cytology does. HPV DNA testing is more sensitive than cytology for detecting CIN2+ and leads to reduced detection of CIN2+ in the subsequent screening round. The 3–10-year risk of CIN3+ is lower after a negative HPV DNA test than after negative cytology.

Harms. HPV DNA testing leads to an increase in the proportion of screen-positive women and colposcopy referrals compared with cytology, which is attenuated by triage testing of HPV-positive women. Primary HPV DNA screening with triage testing can be implemented with only a minimal change in the rates of overdiagnosis of CIN2+.

Balance of benefits and harms. The benefits of a reduction in cervical cancer incidence and mortality outweigh the increase in the proportion of positive tests and colposcopy referrals and the potential increase in psychological harms. The balance will be even more favourable after multiple rounds of HPV-based screening because HPV DNA testing programmes enable longer screening intervals than cytology screening programmes do.

7.8 HPV DNA testing alone versus co-testing

HPV DNA testing alone has been compared with co-testing (combined HPV DNA testing and cytology) in a meta-analysis, a joint analysis of cohort studies, four randomized controlled trials, six prospective cohort studies, and retrospective analyses of a large laboratory database. The studies span nearly 15 years and differ with respect to referral strategies, follow-up time, and outcomes examined (CIN2+, CIN3+, and invasive cancer).

Benefits. Co-testing results in about 5% higher sensitivity for the outcomes of CIN2+ and CIN3+ compared with HPV testing alone. There is a lack of data from randomized controlled trials on the efficacy of HPV testing versus co-testing with regard to mortality, and limited data on the end-point of invasive cancer.

Harms. Compared with HPV testing alone, co-testing has a lower specificity for the detection of CIN2+ and CIN3+. Co-testing results in an increase in the rate of referrals for colposcopy and a decrease in the positive predictive value in referred women compared with HPV testing alone. The loss in specificity and the lower positive predictive value of co-testing may lead to increased detection of regressive lesions.

Balance of benefits and harms. The benefits of co-testing do not outweigh the harms. There is a minimal increase in sensitivity with co-testing; however, this gain is small and the impact on cancer incidence is unclear. Furthermore, this difference in sensitivity affects very few cases, suggesting that the relative contribution of the cytology component of co-testing is limited. Over longer follow-up, the cumulative risks of CIN2+ and CIN3+ for co-test-negative women differ minimally from those for HPV-negative women.

Additional considerations. Analysing all samples with cytology and HPV testing, rather than with HPV testing alone, requires far more resources.

7.9 Considerations on related issues

7.9.1 Triage

(a) Triage of HPV-positive women

Triage is used to optimize the balance of benefits and harms of cervical screening with HPV testing. Many triage approaches are feasible, including strategies that involve one-time (reflex) triage testing and two-time (follow-up or delayed) triage, and a range of combinations of technologies are feasible in both contexts. The acceptability of any triage approach is ultimately context-specific and depends on a range of factors, including the underlying risk of CIN3+ and invasive cervical cancer in a population, the available technological options for triage testing, the cost–effectiveness, and the acceptability of the testing process to women. All the triage options considered in the current review enable reaching a positive predictive value for CIN3+ of more than 10%. However, depending on the pre-test prevalence in HPV-positive women and the chosen triage approach, the number of women who must be referred for colposcopy to detect one case of CIN3+ varies from 3 to 9. For the strategies considered here, a negative triage test result was never associated with a risk of CIN3+ of lower than 1%; this might be a reason to keep the woman under further surveillance.

(b) Triage by HPV testing after an ASC-US or LSIL test result

The Working Group considered that HPV testing for women with ASC-US can substantially decrease the number of colposcopies, but that HPV testing for women with LSIL may not be effective in reducing harms in young women,

and that its impact in older women may vary across settings.

(c) Triage with HPV DNA tests versus HPV mRNA tests

The Working Group considered that there was no evidence that using HPV RNA testing as a triage test could increase specificity for CIN2+ compared with HPV DNA testing; there was no indication that the sensitivity of HPV RNA tests for CIN2+ was different than that of HPV DNA tests.

7.9.2 Self-sampling

The Working Group considered that the use of self-sampling approaches for HPV DNA detection provided high values of sensitivity and specificity compared with the use of clinician-collected samples. The higher sensitivity of HPV DNA detection through polymerase chain reaction (PCR) assays may enable the detection of cervical infections as well as vaginal infections, resulting in an improved predictive value compared with less-sensitive tests. The accuracy of self-sampling for the detection of HPV DNA was not device-dependent. The use of self-sampling approaches for HPV RNA detection showed a significantly reduced sensitivity when compared with the use of clinician-collected samples.

The evidence on whether self-collected samples could be used for genotype comparison or other molecular tests remains limited, particularly for the detection of adenocarcinoma and adenocarcinoma in situ. The self-sampling studies had some limitations; in some instances, the diagnostic protocols and workflow were not well documented, because the use of self-sampling was off-label. Thus, the currently available data do not enable quality assessment of self-sampling protocols in scaling up the use of self-sampling. The trade-offs in coverage or participation when self-sampling is being implemented at a large scale will need to be explored further.

7.9.3 Screen-and-treat strategies

The Working Group noted that the observational screen-and-treat studies are very heterogeneous in the design and methodology used, and more data are needed, particularly for HPV screen-and-treat strategies. Self-sampling with rapid on-site HPV testing would enable the development of single-visit screen-and-treat programmes; these would benefit from the high accuracy and reproducibility of HPV testing. The role of extended genotyping to discriminate between the highest-risk and the lowest-risk HPV types needs to be evaluated further in this context, because it would enable treatment to be avoided for women infected with HPV genotypes that very rarely cause cancer but are very common in the population. Other triage strategies that can be conducted on self-collected specimens, such as testing for DNA methylation, could decrease unnecessary treatment, but more evidence is needed.

Automated visual examination is a novel strategy that can provide visual screening or triage with high accuracy and limited investment in infrastructure. HPV self-sampling followed by automated visual examination could provide rapid, high-quality screening and triage with integrated assessment of eligibility for treatment, enabling the introduction of effective cervical cancer prevention programmes in resource-constrained settings.

7.9.4 Interventions to increase participation in screening

Among all strategies reviewed by the Working Group, invitation letters appear to increase participation in screening, although most studies have been carried out in high-income countries. In low- and middle-income

countries, mail systems are often unreliable and specific postal addresses are often lacking, which can limit the effectiveness of invitation letters. Evidence also indicates that educational interventions are effective in increasing screening participation. HPV self-sampling has the potential to increase participation, especially when an opt-out strategy is used. In high-income settings, self-sampling is offered mainly through the mail system, but this method is not feasible in many low- and middle-income countries, as with invitation letters. Outreach and navigation strategies have been demonstrated to be highly effective in increasing screening participation, especially if coupled with HPV self-sampling offered during home visits by community health workers, but implementation of this strategy at a large scale will be dependent on the availability of primary health workers or an equivalent outreach infrastructure. The offer of HPV self-sampling kits

to women routinely attending health centres has been shown to be effective in high-income settings. This strategy is much less dependent on human resources than community outreach and takes advantage of the fact that, in many populations, women are the main health caregivers in households. Although the introduction of HPV testing may help to improve the organization of health systems and programmes (e.g. through laboratory centralization, reduced over-screening, and better adherence to recommendations for screening ages), if HPV testing is not coupled with self-sampling it may face barriers similar to those observed for cytology-based screening. Combination and adaptation of effective strategies to address specific contexts, levels of resources, and socioeconomic groups are needed to increase participation in screening.

ANNEX 1. SUPPLEMENTARY MATERIAL FOR SECTION 4.4.7 TRIAGE OF WOMEN WITH A POSITIVE PRIMARY HPV SCREENING TEST RESULT

The supplementary web-only materials listed below are available from https://publications.iarc.fr/604.

A Working Group of 27 independent international experts, convened by the International Agency for Research on Cancer (IARC) between June and October 2020, reviewed the scientific evidence and assessed the cancer-preventive and adverse effects of various methods of screening for cervical cancer. Cervical cancer is the fourth most commonly diagnosed cancer type in women worldwide, and the fourth most common cause of cancer death in women.

This publication is an important update of the previous *IARC Handbook* on cervical cancer screening (Volume 10, published in 2005). Volume 18 provides evidence-based evaluations of the effectiveness of five methods of cervical cancer screening in reducing cervical cancer incidence and/or mortality. The Working Group also reviewed the body of evidence and provided conclusive statements on the comparative effectiveness of those screening methods that are established to reduce cervical cancer incidence and/or mortality. In addition, the Working Group provided an updated literature review on the determinants of participation in screening programmes and on emerging techniques, as well as on the different categories of women at differential risk and the surveillance strategies for such women.