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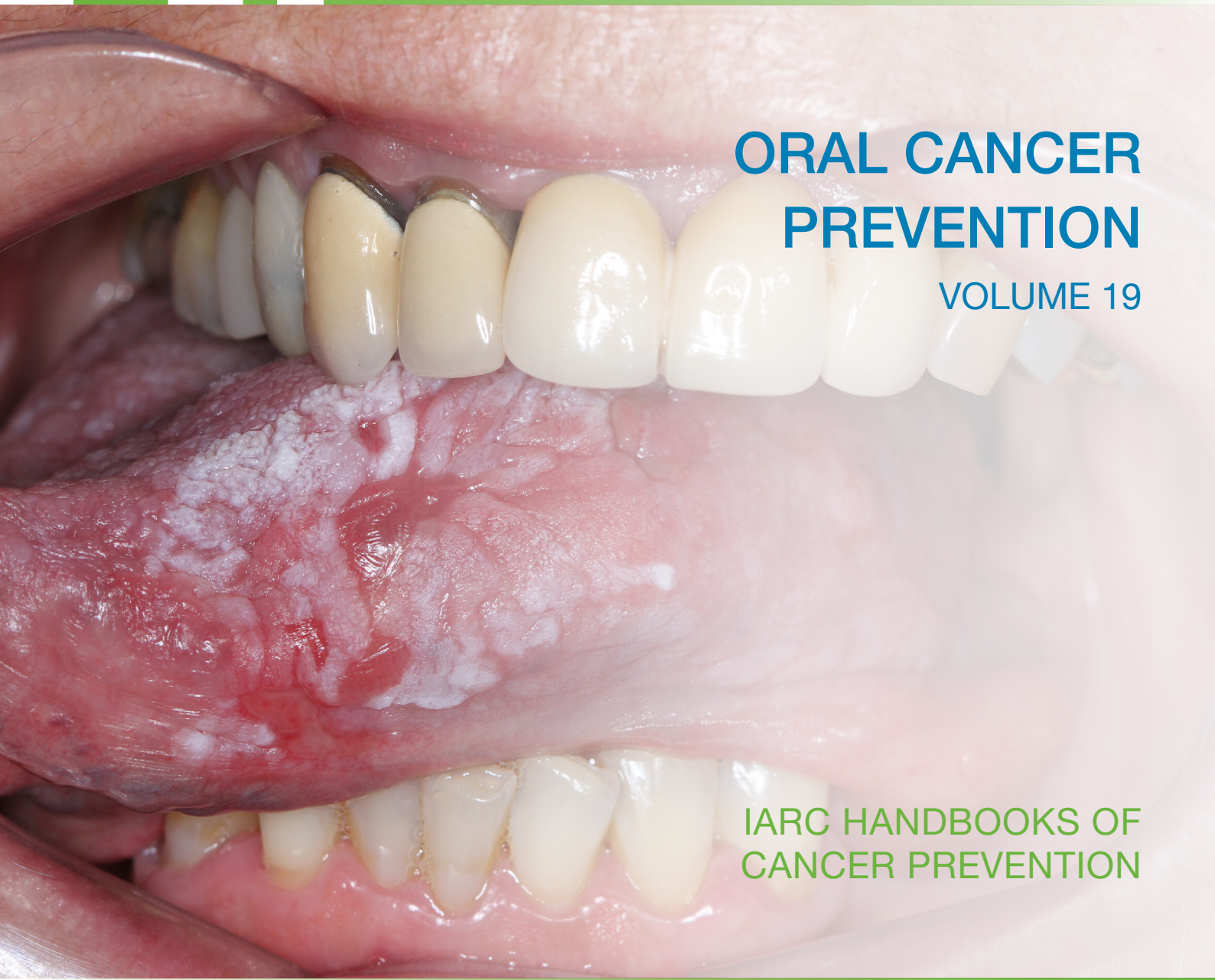


ORAL CANCER PREVENTION

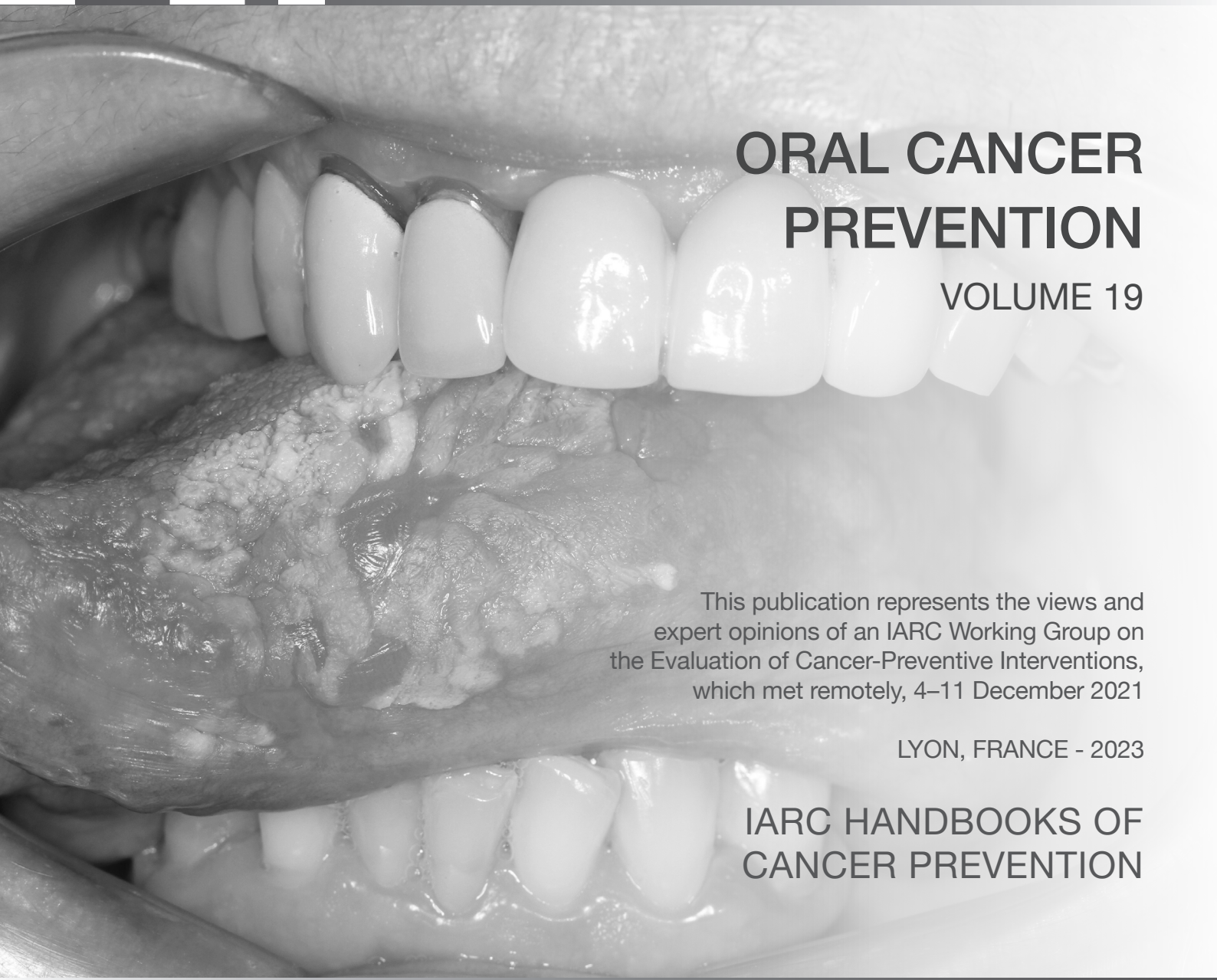
VOLUME 19

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

IARC HANDBOOKS



ORAL CANCER PREVENTION

VOLUME 19

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met remotely, 4–11 December 2021

LYON, FRANCE - 2023

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

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International Agency for Research on Cancer

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/.

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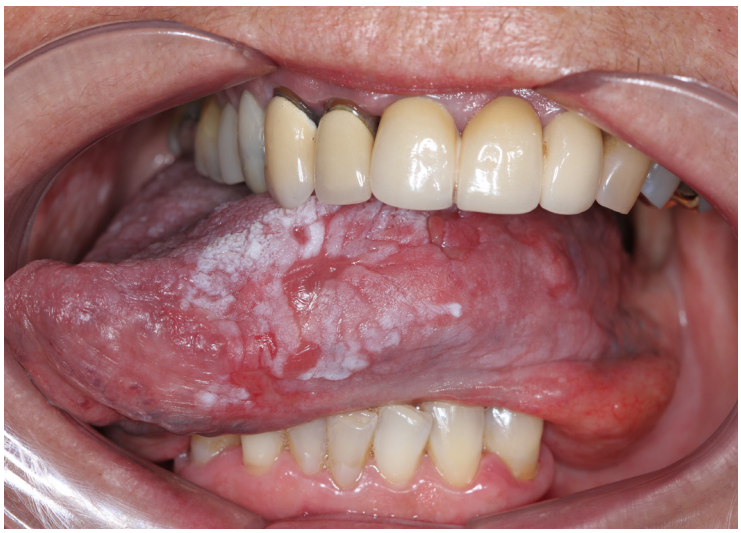

Cover image: Clinical photograph of the mouth of a 72-year-old woman presenting with an extensive, non-homogeneous leukoplakia (with ulcerated areas) on the left lateral border of the tongue, diagnosed by biopsy as a squamous cell carcinoma. © Oral Medicine (Stomatology) Service, OROCENTRO, Piracicaba Dental School, University of Campinas (UNICAMP), São Paulo.

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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, 25 avenue Tony Garnier, CS 90627, 69366 Lyon CEDEX 07, France, or by email to ihb@iarc.who.int, 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.who.int. Corrigenda are published online on the relevant webpage for the volume concerned (IARC Publications: https://publications.iarc.fr/).

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PREAMBLE – PRIMARY 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, 2016), 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 be sufficiently robust to encompass a wide variety of interventions, ranging from broad societal measures to individual behaviour and to chemoprevention.

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, understanding important 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 primary prevention

The current *IARC Handbook* addresses a specific intervention or class of interventions for **primary prevention**. Primary prevention "aims to reduce the incidence of disease by personal and communal efforts" (Porta, 2014). The term "intervention" in this *Handbook* refers to any action aimed at reducing the incidence of cancer in humans. Primary prevention interventions include increasing human exposure to known cancer-preventive agents, reducing human exposure to known cancer hazards, providing means to reduce the effects of exposure to cancer hazards, or otherwise intervening on human pathological states that cause cancer. In broad terms, such interventions include, for example, regulating exposure to carcinogens, administering chemopreventive pharmaceuticals or other agents, vaccinating against cancer-causing infections, modifying the environment (e.g. planting trees or constructing shade structures in areas of high ambient levels of solar ultraviolet radiation), or promoting personal or societal action to increase the prevalence of healthy lifestyles or behaviours or decrease the prevalence of unhealthy lifestyles or behaviours.

Primary preventive 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.

Although the intent of the *IARC Handbooks* is to evaluate interventions, i.e. a dynamic comparison, there will be circumstances under which an evaluation of the association between exposure to an agent and cancer incidence, i.e. a static comparison, is appropriate. In principle, the approaches to scientific review of the relevant studies in this section will not differ between those entailing dynamic interventions and those entailing static exposures. Therefore, in this Preamble the term "intervention" applies to studies of both types, unless specifically stated otherwise.

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 recommending 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, preventive 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.

Other issues to be considered include the cost, cost–effectiveness, affordability, economic efficiency, health equity impact, feasibility, acceptability, relative value, and human rights impact of the intervention. Depending on the specific intervention, some of these issues may be of sufficiently high interest to be reviewed in the *IARC Handbook*.

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 process of the *IARC Handbooks*, 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, IARC defines the intervention and the outcome to be evaluated, according to one of two scenarios:

Scenario 1: evaluation of the effect of a specified *intervention*, that is, an action that results in a change in a potentially preventive exposure, in producing a specified change in *cancer incidence*.

Scenario 2: a two-step evaluative framework from which, for scientific reasons, the level of evidence that an intervention prevents cancer is established by way of an intermediate outcome.

- In Step 1, the effect of a specified intervention on an intermediate outcome, such as exposure to a particular risk factor or preventive factor for cancer in humans, is evaluated (Jonas et al., 2018). Step 1 alone might be taken if it **has been established in authoritative sources** (e.g. the *IARC Monographs* programme) that a change in the intermediate outcome (decreasing exposure to a risk factor or increasing exposure to a preventive factor) reduces the risk of cancer in humans.
- In Step 2, the effect of the change in the intermediate outcome (decrease in exposure to the risk factor or increase in exposure to the preventive factor) on cancer incidence in humans is evaluated. Evaluation of data streams to support Step 2 alone might be done in preparation for a subsequent evaluation of data to support Step 1 if it **has not yet been established in authoritative sources** that a

change in the intermediate outcome reduces the risk of cancer in humans.

The analytical framework determines whether evidence is reviewed for Step 1 only, Step 2 only, or both Steps 1 and 2. A *Handbook* might, for example, include both Steps 1 and 2 when a systematic review and evaluation of Step 2 is necessary (e.g. is not yet available from other authoritative sources) and the number of studies to be reviewed for Steps 1 and 2 is manageable. Taking Steps 1 and 2 together is equivalent to Scenario 1 with inclusion of one or more intermediate outcomes in the evaluation scheme. The sections below provide additional details on the selection of the interventions and outcomes for review.

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). IARC will also pay attention to topics that extend beyond those covered by other agencies.

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 have not been established formally;
- The available evidence suggests that the intervention has the potential to significantly reduce the incidence of cancer, or to have a significant impact on an intermediate outcome or outcomes known or highly suspected to be linked to cancer (see Section 3.1; see also 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 one or several specific cancer sites or to specific aspects of the preventive intervention (e.g. reduction in excess body fatness) to which the new evidence predominantly relates. 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.

3.3 Selection of the outcomes

In primary prevention of cancer, the outcome targeted by the preventive intervention or interventions is reduction in the incidence of cancer (Scenario 1; see Part A, Section 3.1).

As described above, an intermediate outcome may be chosen as the evaluation outcome for a *Handbook* when there is evidence that a change in the intermediate outcome (decreasing exposure to the risk factor or increasing exposure to the preventive factor) can lead to a reduction in the incidence of one or more types of cancer. An example of such a target is an increase in the smoking cessation rate, which is a commonly used outcome for studies designed to determine the preventive effects of new methods of reducing the incidence of tobacco-caused cancer

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

by way of reducing the prevalence of tobacco smoking. Other examples of changes in intermediate outcomes include a decrease in excess body fatness, a decrease in the levels of diesel engine emissions in urban environments, and an increase in the population coverage of human papillomavirus (HPV) vaccination.

Alternatively, a *Handbook* could, as a first step, evaluate the evidence that changing the intermediate outcome can lead to a reduction in the incidence of one or more types of cancer if such evidence is not already available from authoritative sources, followed by an evaluation of the effect of an intervention on the intermediate outcome (Scenario 2, Step 2 followed by Step 1; see Part A, Section 3.1). An example of such a scenario is evaluation of the evidence that reducing consumption of alcoholic beverages reduces incidence of alcohol-related cancer or precancer, followed by evaluation of the efficacy or effectiveness of a specific intervention in reducing the consumption of alcoholic beverages.

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 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). 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 or affect; 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 interest 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 interest, for transparency and to provide an opportunity for undeclared conflicts of interest 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

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

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.

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 2–6 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 pertinent reports and reviews on: use of the intervention targeted directly to cancer or to a relevant intermediate outcome or outcomes; all experimental and observational studies in humans (including systematic reviews and meta-analyses) of the putative effect of the intervention or interventions on cancer incidence or a relevant intermediate outcome, and any related harms; all relevant experimental studies in animals; and all relevant mechanistic studies.

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, and encompasses the inclusion of studies in humans, studies in experimental animals, and mechanistic studies when relevant, 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 pharmaceuticals), 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 2–4. 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 2–4. 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 2.1d.

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 is described in terms given in Part B, Sections 6a–c for each stream of evidence. The Working Group then integrates the strength-of-evidence conclusions from all streams of evidence (see Part B, Section 6d) and develops the rationale for its overall consensus evaluation of the cancer-preventive effect of the intervention (see Part B, Sections 6d–e).

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 5), using the *IARC Handbooks* criteria (see Part B, Section 6a–c).

(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, Sections 6a–c), 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 6d.

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. Intervention and outcome characterization

An intervention for primary cancer prevention has been defined in this Preamble to be any action aimed at reducing the incidence of cancer in humans (Part A, Section 2). Given this definition, the efficacy or effectiveness of an intervention would be most directly approached by research that examines whether the delivery of the intervention results in a measurable change in a cancer-related exposure that leads to a reduction in the incidence of cancer. However, such research is often lacking, and therefore the possibility of cancer-preventive effects has often been inferred from static associations of cancer incidence with prevalence of exposure to cancer-causing agents or cancer-preventive agents. For example, all measures that are now taken to minimize environmental exposure to asbestos (e.g. regulation of removal of asbestos from buildings or demolition of buildings known to contain asbestos) are based on the very strong evidence that people who have had identifiable exposure to asbestos have a higher incidence of cancer than people who have not had such exposure. Similarly, the evaluation of *Handbooks* Volume 16 that there "is *sufficient evidence* in humans for a cancer-preventive effect of absence of excess body fatness" is almost exclusively based on the substantial body of evidence that cancer incidence is lower in people without excess body fatness than it is in people with excess body fatness; this is a static comparison, not a dynamic comparison as the term "intervention" implies.

1.1 Intervention characterization

This section provides informative background on the intervention and the factors that mediate it. It also summarizes the prevalence and level of the intervention across geographical areas and across the life-course. Methods used to assess exposure to the intervention in key experimental and observational epidemiological studies are described and evaluated. This section also reports on validated biomarkers of internal exposure, metabolites, or other intermediate outcomes that are routinely used for exposure assessment. Concepts of absorption, distribution, metabolism, and excretion, where relevant, are considered in the section on mechanistic evidence (see Part B, Section 4b).

(a) Identification of the intervention

The intervention being evaluated is unambiguously identified. The information provided will vary widely depending on the type of intervention but should be sufficient to enable the implementation of an intervention in practice with reasonable confidence that its outcomes in populations would be similar to those of the intervention from which the bulk of the evidence evaluated in the *Handbook* originated.

Many interventions are multifaceted and comprise complex sets of actions. Interventions determined by personal behaviour or circumstances may result from, be influenced by, or be correlated with a diverse range of behavioural and environmental factors, such as smoking, alcohol consumption, diet, sleep and physical activity patterns, remoteness of residence, and socioeconomic circumstances. The description of such interventions should include their variability across human populations and environments, and their known relationships with other health-determining factors.

(b) Global occurrence and use

Geographical patterns and time trends in occurrence are summarized. A concise overview of quantitative information about sources, prevalence, and levels of individual and population interventions, whether purposive or incidental, is provided. Representative data from formal environmental or behavioural monitoring or surveillance data, research studies, government reports and websites, online databases, and other

citable, publicly available sources are tabulated. Data from low- and middle-income countries are sought and included to the extent that is feasible; information gaps for key regions are noted.

If available, data are reported by region and by other relevant characteristics, such as sex, age, socioeconomic status, and other variables considered relevant by the Working Group.

(c) Regulations and guidelines

Regulations or guidelines that have been established for the intervention (e.g. permissible levels of fortification in food, national dietary guidelines) are described and may be tabulated if they are informative for the interpretation of current or historical levels of the intervention. Information on applicable populations, the basis for regulation, and the timing of regulation may be noted.

(d) Intervention assessment in key epidemiological studies

Epidemiological studies reviewed in the context of the *IARC Handbooks* programme evaluate cancer prevention interventions (or effects on intermediate outcomes) by comparing outcomes across groups differently exposed to changes in a putative cancer-preventing intervention. Therefore, the type and the quality of intervention assessment methods used are key considerations when interpreting study findings. This section summarizes and critically reviews the intervention assessment methods used in both experimental and observational epidemiological studies that contribute data relevant to the *Handbooks* evaluation.

All interventions have two principal dimensions: (i) dose (sometimes defined as concentration or intensity), and (ii) time considerations, including duration (time from first to last exposure), pattern or frequency (whether continuous or intermittent), and windows of susceptibility. This section considers how each of the key epidemiological studies characterizes these dimensions. Interpretation of information for chemical, biological, or physical interventions may also be informed by consideration of mechanistic evidence on absorption, distribution, metabolism, and excretion (e.g. as described in Part B, Section 4b).

In experimental epidemiological studies, the investigators determine, usually by way of randomization, who will and who will not be assigned to the intervention; however, in practice the assignment is not always adhered to. Therefore, a critical assessment of such studies requires careful evaluation using appropriate guidelines or assessment frameworks (e.g. fidelity to intervention implementation and extent of non-adherence to intervention).

Intervention intensity and timing in observational epidemiological studies can be characterized by using environmental monitoring data, records from workplaces or other sources, and subject or proxy reports collected by way of questionnaires or interviews. Both objective and subjective data sources are used, individually or in combination, to assign levels or values of an intervention metric to members of the study population.

Key epidemiological studies with interventions on cancer or intermediate outcomes are identified, and the intervention assessment approach and its strengths and limitations are summarized in text and tables. The Working Group identifies concerns about intervention assessment methods and their impacts on the overall quality of each study reviewed. The Working Group notes the studies where the information provided to characterize the intervention properly, the adherence to the intended intervention in each arm of experimental studies, or the assessment of the intervention in observational studies is inadequate. The Working Group further discusses the likely direction of bias due to non-adherence or to error in intervention assessment in studies where adequate information is available.

1.2 Outcome characterization

(a) Evaluation of cancer outcomes

The cancers are defined and described in terms of their International Classification of Diseases for Oncology (ICD-O) (IARC, 2019) or International Classification of Diseases (ICD) categories, with other relevant morphological or molecular characteristics where relevant.

Benign neoplasms, pre-neoplastic lesions, malignant precursors, and other end-points closely related to cancer may also be reviewed when they relate to the intervention reviewed and are known to predict the primary cancer outcome. These studies can strengthen evidence from studies of cancer itself. For example, the results of controlled trials of sun protection measures in preventing development of cutaneous melanocytic naevi (which are strong risk factors for development of later cutaneous melanoma) in children provide support for the efficacy of sun protection measures in preventing cutaneous melanoma in adults (Thun et al., 2018).

(b) Evaluation of intermediate outcomes

Potentially relevant intermediate outcomes vary widely across human biology, pathology, and behaviour. (Intermediate outcomes that are biomarkers of early biological effects, which are not topics evaluated in *IARC Handbooks*, are described in Part B, Section 4.) All intermediate outcomes are described as precisely as possible, using an applicable international standard classification (e.g. ICD classification). When, as with some behavioural or physiological risk factors, they can be defined or measured in a range of ways, the definitions that are acceptable for the evaluation are clearly defined and acceptable standards for measurement stated.

When an intermediate outcome is the outcome being evaluated, the evidence base establishing that the intermediate outcome has an established causal or preventive association with cancer incidence is briefly summarized.

In what follows, the term "cancer incidence" refers to the **outcome of a *Handbooks evaluation***, that is, to the incidence of **cancer** or of an **intermediate outcome**, as defined in the analytical framework.

2. Studies of cancer prevention in humans

This section includes all pertinent experimental and observational studies in humans that include cancer or a specified intermediate outcome (if it is the topic of the *Handbook*) as a study outcome. As noted above, only observational studies in which changes in the exposure (i.e. intervention) in relation to the outcome have been analysed will be considered, unless specifically stated otherwise. Among many others, these studies also encompass studies with biomarkers as intervention metrics (Alexandrov et al., 2016). As mentioned above, studies that assess biomarkers of early biological effects are reviewed in Part B, Section 4.

This section includes specification and assessment of beneficial effects, as well as potential harms.

2.1 Assessment of beneficial effects

(a) Types of studies considered

Several types of epidemiological study designs contribute to the evaluation of cancer prevention in humans (Table 3). These studies include experimental studies and different types of observational studies (i.e. cohort, case–control, and ecological). In addition to these types of studies, innovations in epidemiology enable other designs that may be considered in *Handbooks* evaluations. *(b) Identification of eligible studies in humans*

Relevant studies in humans are identified using principles of systematic review as described in Part A and further detailed in the Instructions

Table 3 Types of epidemiological studies that contribute to the evaluation of cancer prevention

Experimental studies	
	• High level of investigator control over assignment to the intervention and non-intervention group • Ideally random assignment, either of individuals or of groups, to the intervention and non-intervention group • Provides evidence for the efficacy or effectiveness of a preventive intervention • Includes a range of quasi-experimental designs in which there is lack of random assignment to the intervention and non-intervention; quasi-experimental studies are often at high risk of bias
Observational (non-experimental) studies	
Cohort	• In a prospective cohort study, information on the intervention and non-intervention is collected from individuals who are then followed up over time to assess subsequent outcomes. Further intervention information may be collected at intervals during follow-up. • In a retrospective cohort study, information on intervention and subsequent outcomes in a defined group of individuals, which was usually recorded for purposes other than research, is accessed after the outcomes have occurred. • Nested within these studies, case–control and case–cohort studies provide efficiency and an opportunity to collect additional intervention information.
Case–control	• In a case–control study, individuals newly diagnosed with the outcome in a defined population and a sample of "control" individuals without the outcome from the same source population and time period are enrolled, and their intervention histories are compared. • Intervention information collected from cases and controls must refer to time before disease onset to reasonably infer a temporal association.
Mendelian randomization	• Mendelian randomization studies are cohort or case–control studies in which an intervention is inferred using appropriate genomic surrogate(s) (Yarmolinsky et al., 2018). • These studies are considered to be less prone to bias than other observational studies because the genomic variants from which intervention is inferred are randomly allocated at conception.
Ecological	• The association between an intervention and an outcome is examined not in individual people but in units of population defined geographically and/or temporally. Uncontrolled confounding is a major issue for ecological studies. • Results from ecological studies can support a hypothesis about an intervention–outcome association or, when taken together with results of case–control and cohort studies, support judgements on causal associations. • Results may be persuasive when population-wide implementation of an intervention leads to changes in cancer incidence or mortality: (a) in several populations, and there is no similar trend in similar populations not, or much less, subject to the intervention (e.g. Hakama, 1983); or (b) in a single population, by use of time series analysis when longitudinal data on both the intervention and the outcome are available (e.g. Bernal et al., 2017).

for Authors provided to each Working Group. Eligible studies include all studies in humans of the association of a putative cancer-preventive intervention with the occurrence of cancer, or a specified intermediate outcome if it is a topic of the *Handbook*. Multiple publications on the same study population are identified so that the number of independent studies is accurately represented. Multiple publications may result, for example, from successive follow-ups of a single trial population or cohort, from analyses focused on different aspects of an intervention–outcome association, or from inclusion of overlapping populations. In these situations, the most recent or most informative report is usually reviewed first, with recourse to the other reports if important information (e.g. methodological detail) is not included in the most recent or most informative report.

(c) Study quality and informativeness

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, and experimental studies are arguably more prone, because of their smaller sample sizes, associated with the greater cost of conducting such studies.

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 intervention and an outcome. Biases that require consideration are varied and can be broadly categorized as selection bias, information bias, 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 intervention status 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 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 intervention with the outcome. 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 still arise as a result of lack of concealment, non-random allocation, lack of blinding, post-randomization exclusions, non-acceptance of or non-adherence by the study participants to the intervention condition of the study arm to which they are randomized, or study loss to follow-up. One potential shortcoming of randomized studies is their potentially limited external validity (relevance) and consequently limited generalizability to non-studied populations.

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

- **Study description:** Clarity in describing the study design, implementation, and conduct, 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 intervention and the outcome. 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 intervention of interest, and the intervention must have been assessed in a way that was not related to outcome status. In these respects, completeness of recruitment into the study from the population of interest (which is less of an issue for experimental efficacy studies than for effectiveness studies and observational studies) 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 1.2) for the 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.
- **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 in experimental studies (see Part B, Section 1.1. Of particular relevance is an assessment of the error associated with the measurement of change over time in several study designs, including prospective longitudinal studies (e.g. change in body weight estimated from contemporary recall of past body weight and self-reported or measured current body weight at recruitment into a cohort study).
- **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, as described in Part B, Section 1d) that could influence the occurrence of the outcome and may be related to the intervention of interest. 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. For example, repeated assessments of exposure to the intervention over time can be influenced by the occurrence of the outcome and thus bias the result and sometimes lead to "reverse causation". All possible sources of bias are considered for their possible impact on the results, including the possibility of reporting bias (selective reporting of some results).
- **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. For example, the use of directed acyclic graphs can inform about whether confounding and selection biases have been specified correctly (Hernán et al., 2004).

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, between the intervention and the outcome in a relevant population, 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 at least moderate heterogeneity of exposure to the intervention (intensity, frequency, and/or duration) in the study population, and biologically relevant definitions of the intervention.

(d) 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, they should comply with basic quality standards for meta-analyses and their underlying systematic reviews (e.g. AMSTAR, 2017): their risk of bias is carefully evaluated, including the completeness of the studies included, the methods used to identify and the criteria used

to select eligible studies, and the accuracy of the data extracted from 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 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.

(e) Considerations in assessing the body of epidemiological evidence

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

After the quality of individual epidemiological studies of cancer or of an intermediate outcome has been assessed and the informativeness of the various studies on the association between the intervention 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 intervention under review prevents cancer in humans. 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 false strong association. 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 outcome is common or if the intervention is highly feasible. Estimates of effects of small magnitude can also contribute useful information if the magnitude of the effect correlates with the level of 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 preventive efficacy or effectiveness than are isolated observations from single studies. If there are inconsistent results among investigations, possible reasons for such inconsistencies are sought – such as differences in time since initiation of the intervention (latency), intervention levels (e.g. dosage), or assessment methods – 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. The likelihood of reverse causation (i.e. the outcome prompts the intervention) is greater in observational studies of interventions, which often entail self-reported behaviour change, than in studies of static exposures.

An observation that cancer incidence decreases with increasing exposure to a putative preventive intervention is considered to be an indication of a preventive effect, although the absence of a graded response is not necessarily evidence against a causal relationship, and there are several reasons why the shape of the intervention–outcome association may be non-monotonic (e.g. Stayner et al., 2003).

Confidence in a causal interpretation of the evidence from studies in humans is enhanced if it is coherent with physiological and biological knowledge, including information about target organ exposure to the intervention, characteristics of tumour subtypes, and evidence of biological mechanisms by which the intervention could exert a cancer-preventive effect (see Part B, Section 4b).

The Working Group considers whether or not there are subpopulations with increased susceptibility to the cancer-preventive effects of the intervention. For example, studies that identify inter-individual differences in cancer susceptibility to the intervention on the basis of sociodemographic characteristics (e.g. age, sex, race, ethnicity), other behavioural factors (e.g. smoking or alcohol consumption), genetic polymorphisms, or age at first intervention (e.g. childhood interventions) may contribute to the identification of cancer-preventive interventions in humans. Such studies may be particularly informative if genetic polymorphisms are found to be modifiers of the intervention–outcome relationship, because evaluation of polymorphisms may increase the ability to detect an effect in susceptible subpopulations. Identifying susceptible subpopulations can also improve the specificity of targeting interventions.

2.2 Harms of the intervention

Potential harms to individuals that are linked to the intervention under review are also reviewed. Evidence of harm may come from any type of epidemiological study and may also be reported separately from evidence on the potential beneficial effects of the intervention. Although the *IARC Handbooks* do not formally evaluate the harms associated with an intervention 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.

There are three broad categories of possible harms associated with interventions: (i) biological harm (e.g. toxicity of a chemopreventive agent), (ii) physical harm (e.g. injury associated with increased physical activity), and (iii) psychosocial harm (e.g. community-based interventions and social marketing campaigns specifically targeting obesity; Walls et al., 2011). Evidence of occurrence of biological, physical, and psychosocial harm (including emerging harms identified using qualitative methods in intervention studies) is reviewed and described, and the potential impacts of the harm are discussed.

Known financial harms or opportunity costs (Walls et al., 2011), which can apply at the individual level (e.g. higher cost of healthy foods, impacts of increases in tobacco taxes on smokers of lower socioeconomic status, membership of a weight-loss plan) or the community level (e.g. community-based interventions and campaigns), may be noted.

2.3 Balance of benefits and harms

Ideally, the benefits and harms of primary prevention interventions are expressed in similar terms, such as quality-adjusted life years (QALYs) gained (benefits) or lost (harms) per 1000 individuals of the target population. After identification of all published estimates of the balance of benefits and harms based on the same combination or combinations of intervention and outcome, the Working Group selects those based on the highest-quality evaluative studies of the intervention, critically assesses each, and summarizes the results, in narrative or tabular format as appropriate. The results do not contribute to the overall evaluation of each intervention, but they may be highlighted in the rationale after the evaluation and can be used to aid decisions about implementation of and participation in the relevant primary preventive interventions.

2.4 Cost–effectiveness

For a primary preventive intervention that can deliver a beneficial outcome, cost–effectiveness is usually expressed as the estimated financial cost of implementing the intervention per unit of benefit it delivers, which is most often measured in terms of QALYs gained. 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). Although most primary preventive interventions come at a net cost to health services, some can deliver a gain in QALYs and a reduction in health service cost (Vos et al., 2010). 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.

Taking a similar approach to that taken for the balance of benefits and harms described above, the Working Group identifies published reports of well-conducted cost–effectiveness analyses based on the highest-quality evaluative studies of the primary preventive intervention, critically assesses each, and summarizes the results, in narrative or tabular format as appropriate. The results do not contribute to the overall evaluation of each intervention, but they may be highlighted in the rationale after the evaluation and can be used by governments and health services to aid decisions about implementation of the intervention for which there is sufficient evidence of a preventive effect. In addition, it is important to note that when the intervention is targeted towards a risk factor for cancer that is also a risk factor for other chronic diseases, any estimate of cost–effectiveness that is based solely on cancer is of limited use for policy purposes.

3. Studies of cancer prevention in experimental animals

(a) Types of study considered

Animal models are an important component of research on cancer prevention. Models are available that enable the evaluation of the effects of interventions on the development or progression of cancer in most major organ sites. Animal models for cancer include: (i) carcinogen-induced (e.g. chemical, physical, or infectious/biological); (ii) genetically engineered; (iii) transplantable systems (e.g. xenograft, organoid); and (iv) spontaneously developing tumours. Most cancer-preventive interventions investigated can be categorized at the biological level as those that: (i) prevent molecules from reaching or reacting with critical target sites; (ii) reduce the sensitivity of target tissues to carcinogens; or (iii) interrupt the evolution of the neoplastic process. There is increasing interest in the use of combinations of interventions as a means

of increasing efficacy and minimizing toxicity; animal models are useful in evaluating such combinations. The development of optimal strategies for intervention in humans can be facilitated by the use of animal models that mimic the neoplastic process in humans. The questions posed below (modified from Lewis et al., 2017) may assist in determining the relevance of individual studies in experimental animals to the evaluation of cancer-preventive effects in humans:

- Are the timing, route, level, and frequency of exposure comparable with those in humans, after accounting for relevant species differences?
- Is the cancer that is induced (i.e. by a biological, physical, or chemical agent, or genetic manipulation) relevant to the cancer in humans?
- Is the time at which the outcome is assessed relevant and justified?
- Does the study explore only mechanisms or pathways of cancer development?
- Is the outcome measure cancer incidence or progression rather than surrogate measures of tumour activity, such as tumour size or number of tumours?
- Do the outcome measures mimic those being evaluated in humans? More specifically, does the tumour mimic the human disease in terms of the organs or tissues affected, and at the histopathological or genetic level? Does the progression of the disease mimic the cancer in humans?

Relevant studies of cancer in experimental animals are identified using principles of systematic review as described in Part A and further detailed in the Instructions for Authors provided to each Working Group. Consideration is given to all available long-term (i.e. lifetime or near-lifetime) studies of cancer in experimental animals with the intervention under review and, when appropriate, related interventions (see Part A, Section 7). After a thorough evaluation of the pertinent study features (see Part B, Section 3b), studies judged to be irrelevant or inadequate according to the criteria determined in consultation with the Working Group may be excluded. Guidelines for conducting and reporting studies in experimental animals have been published (e.g. OECD, 2018; Percie du Sert et al., 2018).

(b) Study evaluation

Important considerations for assessing study quality include: (i) whether the intervention under review was clearly characterized; (ii) whether the intervention exposure or dose was characterized and monitored adequately; (iii) whether the control animals, exposure doses, duration of dosing, timing and frequency of dosing, duration of observation, and route of exposure to the intervention were appropriate; (iv) whether appropriate experimental animal species and strains were evaluated, including appropriate sex and age; (v) whether there were adequate numbers of animals per group; (vi) whether animals were allocated randomly to groups; (vii) whether all experimental conditions, with the exception of the tested intervention, were identical between the groups; (viii) whether the histopathology review was adequate; and (ix) whether the data were analysed correctly and reported according to well-accepted standards (e.g. Percie du Sert et al., 2018).

Specific factors to be considered in interpreting the results of cancer prevention experiments include: (i) the timing of the intervention over the course of the animals' lifespan; (ii) the timing and duration of administration of the intervention in relation to any carcinogen administration; (iii) dose–response effects; (iv) the site specificity of the anticipated cancer-preventive outcome; (v) the spectrum and relevance of the preventive outcome, from pre-neoplastic lesions to invasive cancers; (vi) the incidence, latency, and magnitude of the outcome, and the multiplicity

of the relevant neoplasms and/or other lesions; and (vii) the number and structural diversity of experimental or environmental exposures, and carcinogenic mechanisms underpinning the animals' baseline risk of the cancer to which the intervention was targeted. In addition, because administration of an intervention may result in prevention of tumours at one site but unintended consequences at other sites, it is important that multiple organs are examined in animal experiments.

Because certain factors, including diet, food or water consumption, infection, and stress, may modulate cancer risk, consideration should be given to the potential for interaction between these factors and the intervention being studied.

(c) Statistical considerations

The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). An appropriate unit of analysis should be used (e.g. cage or individual animal in feed studies). The statistical methods should reflect the outcomes of the study (e.g. tumour incidence or multiplicity, or overall survival of the animals). For outcomes other than survival, the potential influence of different overall survival time between exposed and unexposed animals should be considered.

4. Mechanistic evidence and other relevant biological data

For a rational implementation of cancer-preventive measures, it is important not only to assess preventive end-points but also to understand the mechanisms by which the intervention exerts its cancer-preventive action. Mechanistic studies derived from human research and complemented by experimental models support cancer prevention research in humans by providing critical insight into the biological processes that can mediate the relationship between an intervention and a cancer outcome. Studies of mechanisms provide evidence for biological plausibility, inform causality, and can identify biomarkers relevant to the carcinogenic process. The study of mechanistic biomarkers can provide insights into human heterogeneity in response to carcinogens according to age, sex, genetic background, and other variables that are important to the application of cancer-preventive interventions in human populations. This array of possible contributions by mechanistic studies means that outcomes and end-points will vary widely depending on the types of intervention and the specific types of cancer examined in each *Handbook*.

Mechanistic studies and data are identified, screened, and evaluated for quality and human relevance using principles of systematic review, as described in Part A and further elaborated in the Instructions for Authors provided to each Working Group, and as detailed below.

(a) Types of studies considered

This section focuses primarily on studies in humans, including intervention trials and longitudinal studies with cancer-relevant biomarkers that may serve as exposure or intermediate end-points. Data from relevant experimental models may also be incorporated, especially when data from studies in humans are limited or are not practical to obtain.

(b) Evidence of cancer prevention

Possible mechanisms of action of interventions aiming at cancer prevention may include, but are not limited to: (i) altering the absorption, distribution, metabolism, and excretion of a known cancer-promoting or cancer-preventive agent; (ii) reducing endogenous DNA damage (e.g. by decreasing the oxidative stress and DNA–protein cross-links) or activating DNA repair or modulating epigenetic mechanisms;

(iii) altering host physiology, such as the endocrine environment (e.g. by modulation of exogenous ligands, including hormones) or the microbiome; (iv) affecting cell biology to reduce a cell's susceptibility to transformation, initiation, and progression of tumorigenesis (e.g. by regulating cell differentiation, proliferation, migration, invasion, and cell death through apoptosis and senescence); and (v) modifying the tumour microenvironment, including the inflammatory and immune responses. Inter-individual variations in these responses or outcomes associated with host factors such as age, sex, race/ethnicity, and genetic heterogeneity (e.g. metabolic polymorphisms) are also considered.

In the case of potentially chemopreventive agents, studies of absorption, distribution, metabolism, and excretion in humans and other mammalian species are summarized. The metabolic fate of the intervention agent is described, noting the metabolites that have been identified and their reactivity. A metabolic schema may indicate the relevant metabolic pathways and products, and whether supporting evidence is derived from studies in humans, in experimental animal systems, or in in vitro models. When available, physiologically based pharmacokinetic models and their parameter values are included.

(c) Harms of the preventive intervention

Any intervention that has putative beneficial effects must be assessed for potential harms. Toxic and other potentially harmful effects of a cancer-preventive intervention that are observed in studies in humans or studies in experimental animals and that might predict harmful effects in humans are reviewed, and the relevant evidence about them is summarized.

(d) Study quality and evidence synthesis

The Working Group summarizes the studies, with an emphasis on characterizing consistencies or differences in results within and across studies of varying experimental designs and model systems. Based on considerations of the quality of the studies (e.g. design, methods and reporting of results, as described in Part B, Section 3b) and relevance to humans, the Working Group may give greater weight to some included studies.

Evaluation of the results of studies in humans includes consideration of study quality, as discussed in Part B, Section 2. For observational and other studies of mechanisms of cancer prevention in humans, the quality of the study design, the intervention exposure assessment, and the accuracy (validity and precision) of the biomarker measurement are considered, as are other important factors, including those described for the evaluation of studies of cancer prevention in humans (Vermeulen et al., 2018). Specific guidelines to assess the quality of molecular biomarker and genetic studies are given in STROBE-ME (Gallo et al., 2011) and STREGA (Little et al., 2009), respectively.

In addition to studies in humans, mechanistic insights may be complemented by studies in experimental systems, including animal models (Le Magnen et al., 2016) and in vitro studies. Important considerations for in vitro studies include the ability of the system to recapitulate the carcinogenic process that occurs in humans and to model the exposure of the intervention as would be experienced in vivo (Lewis et al., 2017; Gordon et al., 2018).

The synthesis is focused on the evidence that is most informative for the overall evaluation. Evidence from several streams of mechanistic data, especially those from studies in humans, can strengthen mechanistic conclusions.

5. Summary of data reported

(a) Intervention characterization

The nature of the intervention and its characteristics, common use, and implementation in different settings, including geographical patterns and time trends, are summarized as

appropriate depending on the intervention under review. Intervention assessment methods used in key epidemiological studies reviewed by the Working Group, their strengths, and their limitations are also summarized.

(b) Cancer prevention in humans

Results of epidemiological studies pertinent to an evaluation of the cancer-preventive effects of the interventions and their harms in humans are summarized. The overall strengths and limitations of the epidemiological evidence are highlighted to indicate how the evaluation was reached. The target organ(s) or tissue(s) in which a decrease in cancer occurrence was observed are identified. Intervention–outcome associations and other quantitative data may be summarized when available. When the available epidemiological studies pertain to a mixed intervention (e.g. fruits and vegetables), the Working Group may seek to identify the specific agent or group of agents most likely to be responsible for any cancer-preventive effect. The evaluation is focused as narrowly as is appropriate or as the available data permit. Summaries of the evidence on the balance of benefits and harms and on cost–effectiveness are also provided.

(c) Cancer prevention in experimental animals

Results pertinent to an evaluation of a cancer-preventive effect in animals are summarized to indicate how the evaluation was reached. For each animal species and study design, it is stated whether or not changes in overall survival or tumour incidence, latency, severity, or multiplicity were observed, and the tumour sites are indicated. Dose–response patterns are also summarized. Possible harms of the intervention are noted.

(d) Mechanistic and other relevant data

Results pertinent to mechanisms of cancer prevention are summarized. The summary encompasses the informative studies on cancer-preventive mechanisms with adequate evidence for evaluation, and on any other aspects of sufficient importance to affect the overall evaluation. High-quality studies in humans, when available, are prioritized. In addition, supporting findings from experimental animal models or in vitro systems are summarized, especially when data from studies in humans are limited.

6. Evaluation and rationale

Evaluation of the evidence is guided by an analytical framework that depicts the relationships among the population, intervention, comparator, and outcomes (including both benefits and harms), and key contextual issues related to adherence to and implementation of the intervention and its impact on population health. The analytical framework may articulate both direct pathways (the intervention has a direct effect on cancer outcomes) and indirect pathways (the intervention has an effect on an intermediate outcome that has an established causal or preventive association with cancer incidence).

Consensus evaluations of the strength of the evidence of cancer-preventive effects of the intervention in humans, in experimental animals, and in mechanistic studies are made using transparent criteria and defined descriptive terms (see below). The Working Group then develops a consensus overall evaluation of the strength of the evidence that the intervention under review prevents cancer and assigns the intervention to one of four categories (see below).

When the Working Group has reviewed multiple, closely related interventions (e.g. different forms of an intervention on the same presumed cause of cancer), they may be grouped together for the purpose of a unified evaluation

of the strength of the evidence that they prevent cancer.

The framework for these evaluations, described below, may not encompass all factors relevant to a particular evaluation of preventive effect. After considering all relevant scientific findings, the Working Group may, exceptionally, assign the intervention to a different category from the one that a strict application of the framework would indicate, while providing a clear rationale for the overall evaluation reached.

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 prevent cancer in humans. Consideration may be given to how strongly or weakly the intervention can prevent cancer. In addition, actual and potential harms of the proposed intervention are addressed qualitatively and quantitatively, as the evidence base permits.

In what follows, the term "cancer prevention" refers to the **outcome of a *Handbooks* evaluation**, that is, to a **cancer outcome** or an **intermediate outcome**, as defined in the analytical framework. Thus, the wording of these evaluations is the same when an intermediate outcome, not cancer itself, is the outcome studied. As noted above, evaluation of an intermediate outcome is performed only when the intermediate outcome has an established causal or preventive association with cancer incidence.

(a) Cancer prevention in humans

Cancer-preventive effects in humans are evaluated on the basis of the principles outlined in Part B, Section 2. The evidence relevant to cancer prevention in humans is classified into one of the following categories:

Sufficient evidence of cancer prevention in humans: A causal preventive association between the intervention and cancer in humans has been established. That is, a cancer-preventive association has been observed consistently in the body of evidence (including several high-quality studies) and chance, bias, and confounding as causes of this association were ruled out with reasonable confidence.

Limited evidence of cancer prevention in humans: A causal preventive association between the intervention and cancer in humans is plausible. That is, a cancer-preventive association has been observed in the body of evidence, but chance, bias, or confounding as causes of this association could not be ruled out with reasonable confidence.

Inadequate evidence of cancer prevention in humans: The current body of evidence does not enable a conclusion to be drawn about the presence or absence of a preventive association between the intervention and cancer in humans. Common situations that lead to a determination of *inadequate evidence of cancer prevention in humans* include: (a) no data are available in humans; (b) there are studies available in humans, but of poor quality or informativeness; and (c) there are studies available in humans of sufficient quality, but their results are inconsistent or otherwise do not enable a conclusion to be drawn.

Evidence suggesting lack of cancer prevention in humans: There are several high-quality studies covering, through direct or indirect pathways, the full range of levels of the intervention that humans are known to encounter that are mutually consistent in not showing a preventive association between the intervention and the studied cancers at any observed level of intervention. The results from these studies alone or in combination had narrow confidence intervals with their upper bounds above or close to the

null value (e.g. a relative risk of 1.0). Similarly, bias and confounding as possible causes of this null result were ruled out with reasonable confidence, and the studies were considered informative. A conclusion of *evidence suggesting lack of cancer prevention in humans* is limited to the cancer sites, populations, life stages, conditions and levels of intervention, and length of observation covered by the pertinent studies. The target organ(s) or tissue(s) where evidence suggesting of lack of cancer prevention was observed in humans are identified.

(b) Cancer prevention in experimental animals

Cancer-preventive effects in experimental animals are evaluated on the basis of the principles outlined in Part B, Section 3. The evidence relevant to cancer prevention in experimental animals is classified into one of the following categories:

Sufficient evidence of cancer prevention in experimental animals: A preventive association has been established between the intervention and increased cancer-related survival, decreased incidence, increased latency, and/or decreased multiplicity of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in several independent, high-quality studies and model systems.

Limited evidence of cancer prevention in experimental animals: The data suggest a preventive association between the intervention and cancer in experimental animals. That is, an association has been observed but the data are limited for making a definitive evaluation because: (a) the evidence of a cancer-preventive association is based on only a few high-quality studies; (b) the intervention decreases incidence, increases latency, and/or decreases multiplicity only of benign neoplasms; or (c) there are unresolved questions about the adequacy of the design, conduct, or interpretation of the available studies.

Inadequate evidence of cancer prevention in experimental animals: The studies cannot be interpreted as showing the presence or absence of a preventive association between the intervention and cancer in experimental animals because of major qualitative or quantitative limitations of the data available, or no data are available on cancer in experimental animals.

Evidence suggesting lack of cancer prevention in experimental animals: Evidence from high-quality studies in several experimental models shows that, within the limits of the tests used (e.g. tumour site, age at intervention, conditions and levels of intervention tested), the intervention has no preventive association with cancer in experimental animals.

(c) Mechanistic evidence

Mechanistic studies are evaluated on the basis of the principles outlined in Part B, Section 4. The mechanistic evidence is classified into one of the following categories:

Strong mechanistic evidence: There are a substantial number of high-quality studies in humans that consistently link the intervention to a mechanistic pathway by which it could prevent cancer.

Limited mechanistic evidence: The evidence from mechanistic data in humans is suggestive of a cancer-preventive effect of the intervention, but (a) there are a limited number of high-quality studies, or (b) the studies cover a narrow range of experiments or relevant end-points, or (c) there are some inconsistencies in studies of similar design, or (d) there is unexplained incoherence across studies of different end-points, or (e) the available data are limited to studies in experimental model systems.

Inadequate mechanistic evidence: The evidence from mechanistic data in both humans and experimental model systems is lacking, or the data are inconsistent in linking the intervention to any mechanistic pathway by which it could prevent cancer.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole. Overall evaluation of the intervention is a matter of scientific judgement that reflects the strength of the evidence derived from the studies reviewed. The levels of evidence from studies in humans, mechanistic data, and studies in experimental animals are weighed into the overall evaluation, and statements are made about cancer prevention in humans with the wording of one of the standard categories as described below.

One of the two overall evaluation scenarios (see Part A, Section 3.1) will apply, depending on the nature of the evidence that has been reviewed (Table 4; see also Part A). If, for logistic reasons, evidence for Step 1 and Step 2 of Scenario 2 has been reviewed at two separate *Handbooks* meetings, no overall evaluation will be made for Step 2 alone.

None of these evaluations quantify the fraction of the burden of a particular cancer that a specific intervention would prevent; thus, some interventions may prevent a small fraction of the cancer, some may prevent a larger fraction, and these fractions may vary across populations, for example as a function of the prevalence of the relevant risk factors.

Overall evaluation categories

(i) The intervention *is established to prevent cancer in humans* (Group A)

This category is used for interventions for which there is *sufficient evidence* of cancer prevention in humans, either directly (Scenario 1) or in two steps (Scenario 2): from the intervention to the intermediate outcome (Step 1) and from the intermediate outcome to cancer (Step 2).

The organ sites on which the evidence in humans is based are stated here. A statement is also made of what the Working Group considers to be the magnitudes of the benefits and the harms of the intervention, in as nearly comparable terms as possible, for people adhering to the intervention as commonly implemented in practice, and whether or not the benefits outweigh the harms.

(ii) The intervention *probably prevents cancer in humans* (Group B1)

In Scenario 1, this category is used for interventions for which there is *limited evidence* of cancer prevention in humans and either *strong mechanistic evidence* in humans or *sufficient evidence* in experimental animals with all the criteria for the relevance to humans being met (see Part B, Section 3a).

In Scenario 2, this category is used for interventions for which there is *sufficient evidence* in humans that the intervention has a cancer-preventive effect on the intermediate outcome (Step 1), *limited evidence* that the intermediate outcome has a cancer-preventive effect in humans (Step 2), and either *sufficient evidence* in experimental animals with all the criteria for the relevance to humans being met or *strong mechanistic evidence* in humans (see Part B, Section 3a). Alternatively, this category is used when there is *limited evidence* in humans that the intervention has a cancer-preventive effect in the intermediate outcome (Step 1) and *sufficient evidence* that the intermediate outcome has a cancer-preventive effect in humans (Step 2).

(iii) The intervention *possibly prevents cancer in humans* (Group B2)

In Scenario 1, this category is used for interventions for which there is *limited evidence* of cancer prevention in humans, *less than strong evidence* from mechanistic data, and *less than sufficient evidence* of cancer prevention in experimental animals.

In Scenario 2, this category is used when (i) there is *sufficient evidence* in humans that the intervention has a cancer-preventive effect on the intermediate outcome (Step 1), and *limited evidence* in humans and *less than sufficient evidence* in experimental animals or *less than strong evidence* from mechanistic data that the intermediate outcome has a cancer-preventive

Table 4 Summary of the strength of the evidence in each evidence stream contributing to the overall evaluation

Scenario 1: Direct evidence that the intervention prevents cancer			
Strength of the evidence that the intervention prevents cancer in humans	**Strength of the evidence from mechanistic studies that the intervention prevents cancer**	**Strength of the evidence that the intervention prevents cancer in experimental animals**	**Overall evaluation**
Sufficient	–	–	Group A
Limited	*Strong*	–	Group B1
Limited	–	*Sufficient*	Group B1
Limited	*Less than strong*	*Less than sufficient*	Group B2
Inadequate	–	–	Group C
Evidence suggesting lack of cancer prevention	–	*Evidence suggesting lack of cancer prevention*	Group D

Scenario 2: Evidence that the intervention prevents cancer by way of an intermediate outcome (risk factor or preventive factor)			
Step 1	**Step 2**[a]		**Overall evaluation**[a]
Strength of the evidence that the intervention decreases exposure to the risk factor or increases exposure to the preventive factor in humans	**Strength of the evidence that decreasing exposure to the risk factor or increasing exposure to the preventive factor prevents cancer in humans**	**Strength of the evidence that decreasing exposure to the risk factor or increasing exposure to the preventive factor prevents cancer in experimental animals or mechanistic studies**[b]	
Sufficient	*Sufficient*[c]	–	Group A
Sufficient	*Limited*	*Sufficient*	Group B1
Sufficient	*Limited*	*Less than sufficient*	Group B2
Limited	*Sufficient*	–	Group B1
Limited	*Limited*	–	Group B2
Inadequate	–	–	Group C
–	*Evidence suggesting lack of cancer prevention*	*Evidence suggesting lack of cancer prevention*	Group D
Evidence suggesting lack of cancer prevention	–	–	Group D

[a] This overall evaluation applies only when evidence from both Step 1 and Step 2 is available. When a *Handbook* evaluates only Step 2, no overall evaluation is made.

[b] Evidence in experimental animals and mechanistic data is considered to be *sufficient* when there is *strong evidence* from mechanistic data (mechanistic studies in humans) or *sufficient evidence* in experimental animals.

[c] The evidence in this category may be considered to be *sufficient* when it is based on observational studies of change in cancer incidence associated with self-reported or observed (by way of time-separated repeated measures) change in the level of a risk factor or preventive factor (e.g. smoking cessation; increase in consumption of fruits and vegetables), OR, exceptionally, studies of variation in cancer incidence with the level of a risk factor or preventive factor measured at one time point.

effect; OR (ii) there is *limited evidence* in humans that the intervention has a cancer-preventive effect on the intermediate outcome (Step 1), and *limited evidence* in humans that the intermediate outcome has a cancer-preventive effect, and any evidence category in experimental animals and mechanistic data.

When the evidence is classified in Group B1 or Group B2, the evaluation is followed by a description of harms, actual and potential.

(iv) The intervention *is not classifiable as to its capacity to prevent cancer in humans* (Group C)

In both Scenario 1 and Scenario 2, this category is used for interventions for which there is *inadequate evidence* in humans, irrespective of the level of evidence from mechanistic data and studies in experimental animals. Interventions that do not fall into any other category are also placed in this category.

(v) The intervention *probably does not prevent cancer in humans* (Group D)

In Scenario 1, this category is used for interventions for which there is *evidence suggesting lack of cancer prevention* both in humans and in experimental animals. In Scenario 2, this category is used when there is *evidence suggesting lack of cancer prevention* both in humans and in experimental animals for the intermediate outcome to cancer, irrespective of the level of evidence for the intervention to the intermediate outcome; or there is *evidence suggesting lack of cancer prevention* for the intervention to the intermediate outcome, irrespective of the level of evidence for the intermediate outcome to cancer.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is summarized so that the basis for the evaluation offered is transparent. It includes concise statements of the principal line or lines of argument that emerged in the deliberations of the Working Group, the conclusions of the Working Group on the strength of the evidence for each stream, 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 evaluations.

In the rationale, the Working Group may draw attention to the fact that actions on the evaluations should be taken in the light of country- or setting-specific circumstances that influence the public health priority, feasibility, and acceptability of programmes based on the interventions evaluated.

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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.

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GENERAL REMARKS

In April 2016, an international group of scientific and public health leaders from 21 countries met in Kuala Lumpur, Malaysia, at the International Conference on Betel Quid and Areca Nut, to identify research needs and discuss strategies to reduce the prevalence of use of betel quid and areca nut, and thereby the incidence of oral cancers related to their use (Mehrtash et al., 2017). Several members of the panel suggested that IARC – in particular, the *IARC Handbooks of Cancer Prevention* – perform a review and an evaluation of the current scientific literature on several aspects of oral cancer prevention, with a specific focus on South-East Asia.

Volume 19 of the *IARC Handbooks of Cancer Prevention* series provides a first-time evaluation of primary and secondary prevention approaches for oral cancer. The expert knowledge summarized in this *Handbook* will play a major role as a resource for policy-makers involved in the regulation of smokeless tobacco and will help fight a major public health problem. In addition, this *Handbook* aligns with the World Health Organization (WHO) mission of tobacco control, including the WHO Framework Convention on Tobacco Control (FCTC), and with IARC's mission of cancer research for cancer prevention with a particular focus on low- and middle-income countries.

History of use of smokeless tobacco and areca nut

Smokeless tobacco was originally used by the Indigenous populations of South America for various purposes, including in spiritual ceremonies, as a poultice with potential therapeutic effects, and as an exchangeable good (Shafey et al., 2009). In the 15th century, Columbus brought tobacco from his transatlantic expeditions to Europe (Shafey et al., 2009). By the mid-16th century, adventurers and diplomats such as Nicot began to popularize its use, with the introduction of tobacco in France in 1556, Portugal in 1558, Spain in 1559, and England in 1565 (CNN.com, 2000). In India, tobacco was introduced by the Portuguese in the 17th century (Prasad, 2007). Despite changes in consumption patterns with the global spread of tobacco through the centuries (from smokeless tobacco in the 18th century to cigars in the 19th century and cigarettes in the 20th century), tobacco is still currently used in a smokeless form (Shafey et al., 2009).

The chewing of areca nut is deeply embedded in the sociocultural history of South-East Asia and many parts of the Western Pacific. It is mentioned in the *Mahāvamsa*, a historical chronicle of Sri Lanka written in 504 BCE (Krenger, 1942), and in ancient writings of Hinduism in about 600 BCE (Bhishagratna, 1907) and in

writings of mainland China during the Tang dynasty (7th to 9th centuries CE). Cultivation of the *Areca catechu* palm tree has been widespread across South-East Asia and South Asia for millennia, initially in the Philippines and then gradually spreading across the Western Pacific Islands.

Distinguishing between smokeless tobacco products

Oral smokeless tobacco products are traditionally sold in various forms, but they can be broadly categorized as snuff (powdered or ground tobacco) or chewing tobacco (leaf, plug, or twist) (Stanfill et al., 2011). Smokeless tobacco products may contain different concentrations of tobacco-specific *N*′-nitrosamines, depending on their preparation and processing (NCI and CDC, 2014). *N*′-nitrosonornicotine (NNN), one of the most abundant tobacco-specific *N*′-nitrosamines, is formed by *N*-nitrosation of tobacco alkaloids, particularly during tobacco curing; NNN is classified by the *IARC Monographs* as carcinogenic to humans (Group 1) (IARC, 2007; Ammann et al., 2016). The water content of smokeless tobacco products also varies; the water content of chewing tobacco (which ranges between 7% and 21%) is lower than that of moist snuff but higher than that of dry snuff (IARC, 2007). The variation in water content under the same manufacturing and storage conditions has the potential to influence the level of NNN.

Despite the differences between smokeless tobacco products and the potential differences in toxicant exposure and carcinogenic potential, most epidemiological studies do not distinguish between smokeless tobacco products, and this makes it difficult to evaluate cancer risks by product type. For the same reason, the Working Group's evaluation of smokeless tobacco (without areca nut) does not distinguish between outcomes by type of smokeless tobacco and includes both oral snuff and chewing tobacco products.

Distinguishing between products that contain smokeless tobacco or areca nut or both

Smokeless tobacco and areca nut may be used either on their own or in combination. Thus, the resultant products may be categorized as containing only smokeless tobacco, only areca nut, or both smokeless tobacco and areca nut. However, a lack of clarity in reporting (Theilmann et al., 2022) the product categories has been observed in many studies, possibly leading to inappropriate interpretation and evaluation of the evidence. For example, in many studies, products that contain both smokeless tobacco and areca nut are reported as smokeless tobacco (or chewing tobacco). In other instances, the presence or absence of tobacco in the betel quid – a preparation that always contains areca nut – is not specified. In both cases, identification of the specific product(s) relies heavily on knowledge of the practices in the region(s) where the study was conducted (Gupta and Warnakulasuriya, 2002). Hence, it is essential that either the correct **product category** (as mentioned above) is specified or the **specific products** are clearly listed in the study details.

Differences in cessation interventions among youth and adults

The impact of an intervention to quit use of smokeless tobacco or areca nut on adults and youth differs because of age, perception of health risks associated with tobacco use, and the impact of tobacco advertising. Initiation of use is mainly at ages 13–14 years, and most of the initiation

happens before age 18 years. There is a paucity of data in the literature on the efficacy of interventions in preventing initiation of use. Also, young people generally do not perceive that tobacco kills or causes serious diseases. Hence, interventions based on communicating long-term health risks may not be salient to adolescents. However, attitudes and behaviours regarding tobacco use among youth are influenced by advertising in any form. Although performing such an evaluation was outside the scope of this *Handbook*, mass media anti-tobacco advertisements in the form of audiovisual spots, radio spots, print media, and educational awareness campaigns can be effective in promoting cessation.

Framework of evaluation of primary prevention interventions

The impact of preventive interventions on risk behaviours may take more than a decade to produce any significant beneficial effect on the future incidence of cancer. For this reason, it is necessary to monitor intermediate outcomes to assess the benefits of quitting risk habits. For this *Handbook*, IARC used the new Preamble, developed in 2019 (IARC, 2019), with a two-step evaluation: step 1 to assess whether a community programme or an intervention directed at an individual leads to cessation of use of smokeless tobacco and/or areca nut, and step 2 to evaluate whether quitting an exposure leads to a reduction in oral cancer incidence or mortality. However, as mentioned above, the lack of consistency in the terminology that has been used in the literature to describe the products prevented the Working Group from making a full evaluation, from intervention to cancer outcome, for any product category or specific product.

Research gaps in oral cancer prevention

Globally, research efforts for oral cancer trail behind those for most other common cancer types. A comprehensive, well-funded research strategy is needed to assess changes in the patterns of oral potentially malignant disorders (OPMDs) and cancer, especially in parts of the world where the burden of oral cancer is increasing. The reasons for the geographical variations in the incidence of oral cancer must be better understood, with a focus on disparities in the socioeconomic status of the global population and lifestyle habits related to use of tobacco, use of areca nut, and alcohol consumption. Research on the association between use of smokeless tobacco or areca nut and oral cancers in lower-middle-income countries is lacking. In addition, new prevention and cessation intervention models need to be developed and tested at the population and individual levels.

The Working Group also identified the following in high-risk populations: a lack of knowledge of signs, symptoms, and risk factors for oral cancer; inconsistencies in the assessment of risk behaviours; and gaps in the technical practice of clinical oral examination. With respect to screening, research gaps include the following: identifying approaches in the population to encourage and sustain participation among the hard-to-reach, high-risk population; assessing the cost–effectiveness of standard clinical oral examination as a screening approach for oral cancer compared with the addition of new point-of-care diagnostics; and improving the overall 5-year survival rate, which remains about 50%. Finally, an increase in research efforts to control the use of smokeless tobacco products, and strict implementation of the WHO FCTC recommendations, are desirable goals to reduce the global burden of oral cancer.

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LIST OF ABBREVIATIONS

ADH	alcohol dehydrogenase
AI	artificial intelligence
AJCC	American Joint Committee on Cancer
ALDH	aldehyde dehydrogenase
ARCAGE	Alcohol-Related Cancers and Genetic Susceptibility in Europe
ASIR	age-standardized incidence rate
ASMR	age-standardized mortality rate
AUC	area under the curve
BMI	body mass index
CI	confidence interval
COE	clinical oral examination
DOI	depth of invasion
EGFR	epidermal growth factor receptor
ENE	extranodal extension
EPIC	European Prospective Investigation into Cancer and Nutrition
EU	European Union
FAD	flavin adenine dinucleotide
FCTC	Framework Convention on Tobacco Control
FVL	fluorescence visualization loss
FVR	fluorescence visualization retained
GATS	Global Adult Tobacco Survey
GSPS	Global School Personnel Survey
GYTS	Global Youth Tobacco Survey
H&E	haematoxylin and eosin
HDI	Human Development Index
HNC	head and neck cancer
HPV	human papillomavirus
HR	hazard ratio
HRME	high-resolution microendoscope
IARC	International Agency for Research on Cancer
ICARE	Investigation of Occupational and Environmental Causes of Respiratory Cancers
ICD-O	International Classification of Diseases for Oncology
IL-6	interleukin 6
INHANCE	International Head and Neck Cancer Epidemiology

LOH	loss of heterozygosity
miRNA	microRNA
MMP-1	matrix metalloproteinase-1
mRNA	messenger RNA
MSE	mouth self-examination
NBI	narrow-band imaging
NIH-AARP	United States National Institutes of Health-American Association of Retired Persons
OCT	optical coherence tomography
OED	oral epithelial dysplasia
OLP	oral lichen planus
OPMDs	oral potentially malignant disorders
OR	odds ratio
OSCC	oral squamous cell carcinoma
OSF	oral submucous fibrosis
PAF	population attributable fraction
PAS	periodic acid–Schiff
PVL	proliferative verrucous leukoplakia
RCT	randomized controlled trial
RERI	relative excess risk due to interaction
ROC	receiver operating characteristic
RR	relative risk
SCC	squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SLT	smokeless tobacco
STEPS	WHO STEPwise Approach to Surveillance
TNF-α	tumour necrosis factor α
TNM	tumour–node–metastasis
UICC	Union for International Cancer Control
WCRF	World Cancer Research Fund
WHO	World Health Organization

1. ORAL CANCER AND ORAL POTENTIALLY MALIGNANT DISORDERS

1.1 Anatomy of the oral cavity and the oropharynx

1.1.1 Anatomy of the oral cavity

The oral cavity is the entrance to the gastrointestinal tract. It is bounded anteriorly by the lips, posteriorly by the faucial arches anterior to the tonsils, laterally by the cheeks (buccal mucosae), superiorly by the palate, and inferiorly by the muscular floor. The space between the labial mucosae of the lips or the buccal mucosae of the cheeks and the teeth is defined as the oral vestibule (labial or buccal vestibule) (Fig. 1.1).

The oral mucous membrane is covered by the stratified squamous epithelium, which comprises four different layers and protects the inside of the oral cavity. The oral mucosa is subdivided into masticatory mucosa (keratinized), lining mucosa (non-keratinized), and specialized mucosa. The mucosa has the capacity to undergo constant regeneration (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

The subsites of the oral cavity are described below according to the International Classification of Diseases for Oncology (ICD-O) coding: lip (C00), tongue (C02), gingivae (C03), floor of the mouth (C04), palate (C05), and buccal mucosa and oral commissures (C06).

(a) Lips

The lips surround the oral aperture, marking the external boundary of the mouth, and are used for speech, mastication, swallowing, and controlling the size of the oral aperture.

The upper lip extends from the inferior border of the nose and laterally up to the nasolabial grooves. The lower lip is bordered by the labiomental groove. The upper and lower lips meet at the oral commissures.

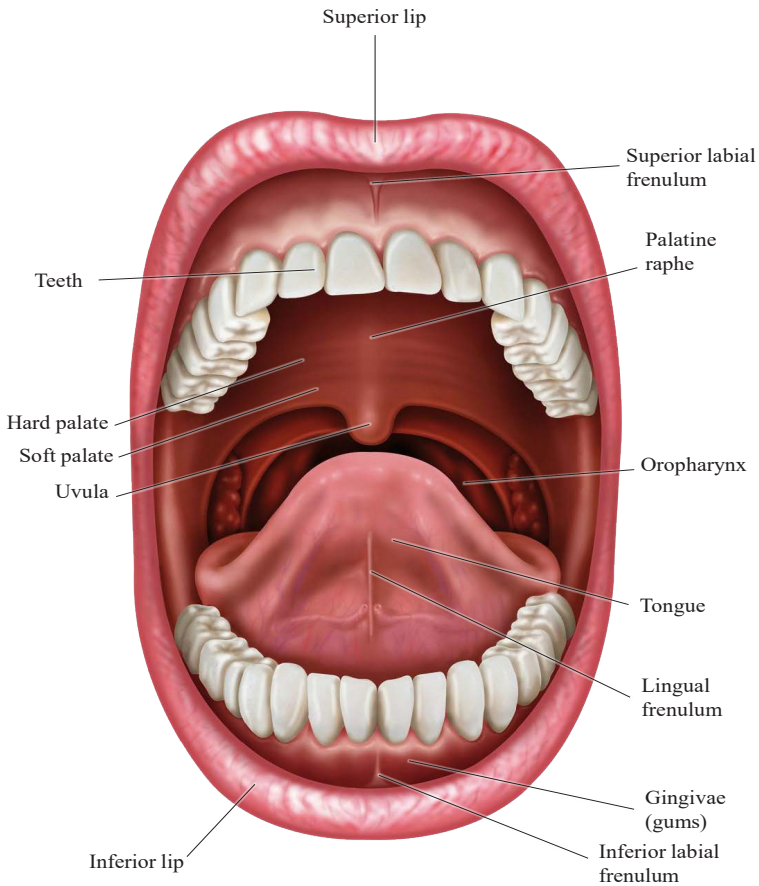
The lips are composed of a muscle that is covered externally by skin and internally by non-keratinized labial mucosa, with the vermilion zone in between. The vermilion zone has keratinized epithelium and is highly vascularized and densely innervated. Numerous mucous glands are present on the labial mucosa. The lymphatic drainage of the lips is primarily to the submandibular lymph nodes and to a lesser extent to the submental, intraparotid, or internal jugular lymph nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(b) Tongue

The tongue is a muscular organ that occupies the floor of the mouth. It is attached to the mandible (lower jawbone) and the hyoid bone by the root. The anterior two thirds of the structure is free to move.

The dorsum is divided into an anterior oral part and a posterior pharyngeal part, which

Fig. 1.1 Anatomy of the oral cavity



forms the base of the tongue. The anterior two thirds of the dorsum is covered by specialized mucosa that contains numerous papillae, some of which bear taste buds. The posterior third slopes down towards the epiglottis and has a nodular appearance because of the underlying lingual tonsils. Two other important anatomical areas of the tongue are the lateral borders and the ventral surface (undersurface) of the tongue.

The extrinsic muscles stabilize and move the tongue, and the intrinsic muscles maintain its shape. The main functions of the tongue are mastication, swallowing, speech, oral cleansing, and taste.

The tongue is highly vascularized; lingual veins are visible on the inferior surface. The anterior two thirds of the tongue drains into the submental and submandibular nodes, which empty into the deep cervical lymph nodes. The posterior third of the tongue drains directly into the deep cervical lymph nodes. The lymphatic drainage is significant because some areas of the tongue drain into bilateral cervical lymph nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(c) Gingivae (gums)

The gingiva is the highly keratinized mucosa that immediately surrounds the neck of an erupted tooth and is firmly attached to the alveolar margins of the jaws. At the gingival crest, the epithelium slopes towards the tooth to form a sulcus and is attached to the tooth surface. The part of the gingiva facing the oral cavity is masticatory mucosa, and the change from alveolar mucosa to gingival mucosa is identifiable by an abrupt colour change of the tissue. Healthy gingiva has some stippling on its surface. The lymphatic drainage of the gingivae is to the submandibular lymph nodes. In addition, the lower anterior gingiva drains into the submental nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(d) Floor of the mouth

The floor of the mouth is a horseshoe-shaped region situated between the movable part of the tongue and the mylohyoid muscles. The lingual frenulum is a mucosal fold that arises near the base of the tongue and extends onto the inferior surface of the tongue. The protuberance at the anterior floor of the mouth is called the sublingual papilla or caruncle; this is where the submandibular salivary ducts open into the oral cavity. On either side laterally and backward are the sublingual folds, which cover the submandibular ducts and the sublingual salivary glands. The covering epithelium is non-keratinized and is much thinner than for other subsites of the oral cavity. The lymphatic drainage is mainly to the submandibular lymph nodes; the anterior part drains into the submental nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(e) Hard palate

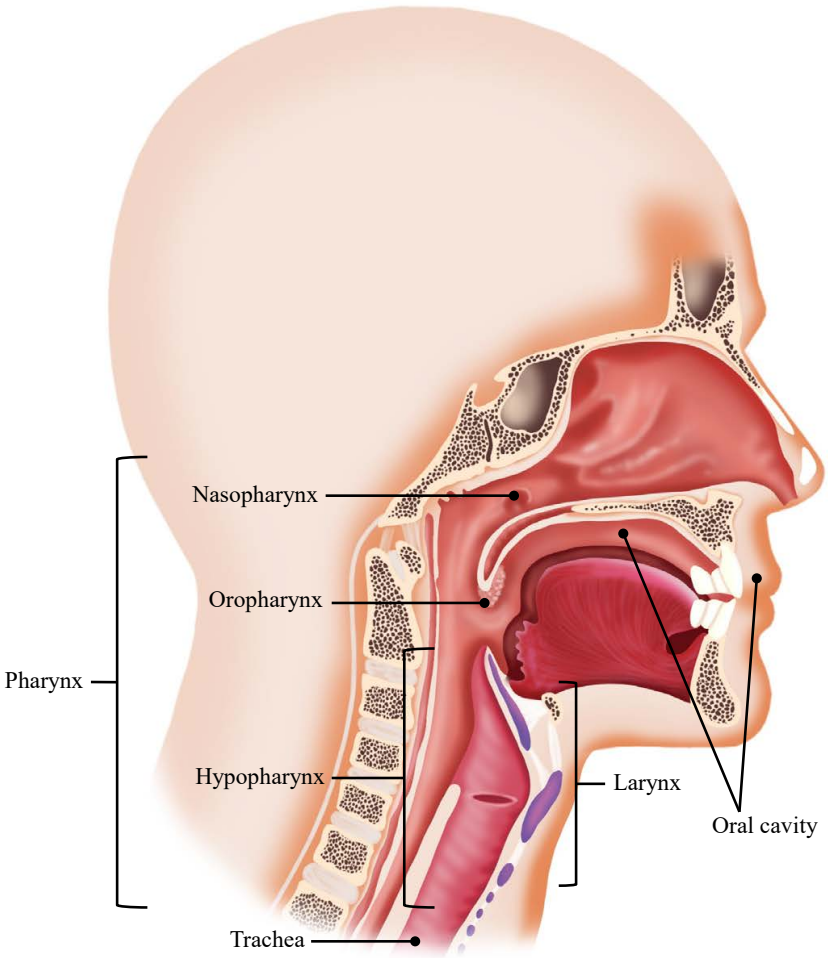
The palate forms the roof of the oral cavity and consists of two parts: the hard palate and the soft palate. The hard palate is part of the oral cavity, and the soft palate is part of the oropharynx.

The palatine processes of the maxillae (upper jawbone) and the horizontal plates of the palatine bones form the hard palate, which is bounded anteriorly by the maxillary teeth (upper teeth) and continues posteriorly to the soft palate. The palatine raphe extends anteroposteriorly in the midline, and an irregular set of rugae radiates from it in the anterior part of the hard palate. The incisive papilla lies at the anterior end of the hard palate, which contains the opening of the incisive canal. The hard palate has a thick keratinized mucosa, which is tightly bound to the periosteum anteriorly and contains minor salivary glands in the posterior submucosa. The lymphatic drainage is primarily to the deep cervical lymph nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

(f) Buccal mucosa

The buccal mucosa is the mucosal lining of the cheeks, extending from the line of contact of the opposing lips to the pterygomandibular raphe. It extends to the line of attachment of the alveolar mucosa superiorly and inferiorly, which forms the anterolateral boundary of the oral vestibule. The buccal mucosa has a non-keratinized epithelium and is firmly attached to the underlying muscle. The submucosa contains minor salivary glands. A white line coinciding with the occlusal plane, called the linea alba, may be present. The parotid ducts of the parotid gland on either side pierce the buccal mucosa opposite the second maxillary molar tooth and present as the parotid papillae. The lymphatic drainage is primarily to the submandibular lymph nodes (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

Fig. 1.2 Anatomy of the pharynx



1.1.2 Anatomy of the oropharynx and the soft palate

The oropharynx is a tube-shaped fibromuscular structure behind the oral cavity, continuous with the nasopharynx superiorly and the hypopharynx inferiorly (Fig. 1.2). The oropharynx has functional roles in both the respiratory system and the digestive system. It extends from the lower surface of the soft palate to the upper border of the epiglottis and communicates with the oral cavity anteriorly. The posterior wall of the oropharynx is formed by the three constrictor muscles. The palatine tonsils project into the lateral wall of the oropharynx from the tonsillar fossa. The oropharynx is covered by a non-keratinized stratified squamous epithelium (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

The soft palate is a mobile flap that extends backward from the hard palate and fuses with the lateral wall of the oropharynx. It is made up of five paired muscles and an aponeurosis. The soft palate can be raised to make contact with the posterior wall of the oropharynx to close off the nasopharynx during swallowing.

The non-keratinized mucosa covers the oral side and the posterior part of the nasal side, and the respiratory mucosa covers the anterior part of the nasal side. The submucosa of both surfaces contains mucous glands and taste buds. Lymphoid follicles are scattered on the oral surface. The uvula hangs down at the midline of the posterior end of the soft palate and helps in phonation (Sinnatamby, 2011; Nanci, 2017; Berkovitz et al., 2018; Standring, 2020).

1.2 Global burden of oral cancer, oropharyngeal cancer, and oral potentially malignant disorders

1.2.1 Oral cancer and oropharyngeal cancer

(a) Global incidence and mortality

Oral cancer, along with oropharyngeal cancer, is among the most common cancer types globally.

In 2020, there were an estimated 377 713 new cases of oral cancer worldwide, with global age-standardized incidence rates (ASIR) of 6.0 per 100 000 men and 2.3 per 100 000 women. There were an estimated 177 757 deaths from oral cancer, with global age-standardized mortality rates (ASMR) of 2.8 per 100 000 men and 1 per 100 000 women.

In 2020, there were an estimated 98 412 new cases of oropharyngeal cancer worldwide, with global ASIR of 1.8 per 100 000 men and 0.4 per 100 000 women. There were an estimated 48 143 deaths from oropharyngeal cancer, with global ASMR of 0.89 per 100 000 men and 0.17 per 100 000 women (Ferlay et al., 2020).

For both oral cancer and oropharyngeal cancer, the incidence increases with age (Fig. 1.3).

(b) Geographical variations in incidence and mortality

In 2020, the incidence rates of oral cancer (including lip cancer) were highest in Melanesia and South Asia (Ferlay et al., 2020; Miranda-Filho and Bray, 2020). The rates (ASIR, per 100 000, in both sexes) were highest in Papua New Guinea (21.2), followed by Pakistan (10.1), India (9.8), Sri Lanka (9.7), and Bangladesh (9.5) (Ferlay et al., 2020). For oral cancer mortality rates, the pattern was similar. The rates (ASMR, per 100 000, in both sexes) were highest in Papua New Guinea (8.3), followed by Pakistan (6.4), Bangladesh (5.6), India (5.4), and Sri Lanka (4.5) (Ferlay et al., 2020) (Fig. 1.4).

Both ASIR and ASMR were consistently higher in men than in women across the world (Ferlay et al., 2020; Miranda-Filho and Bray, 2020).

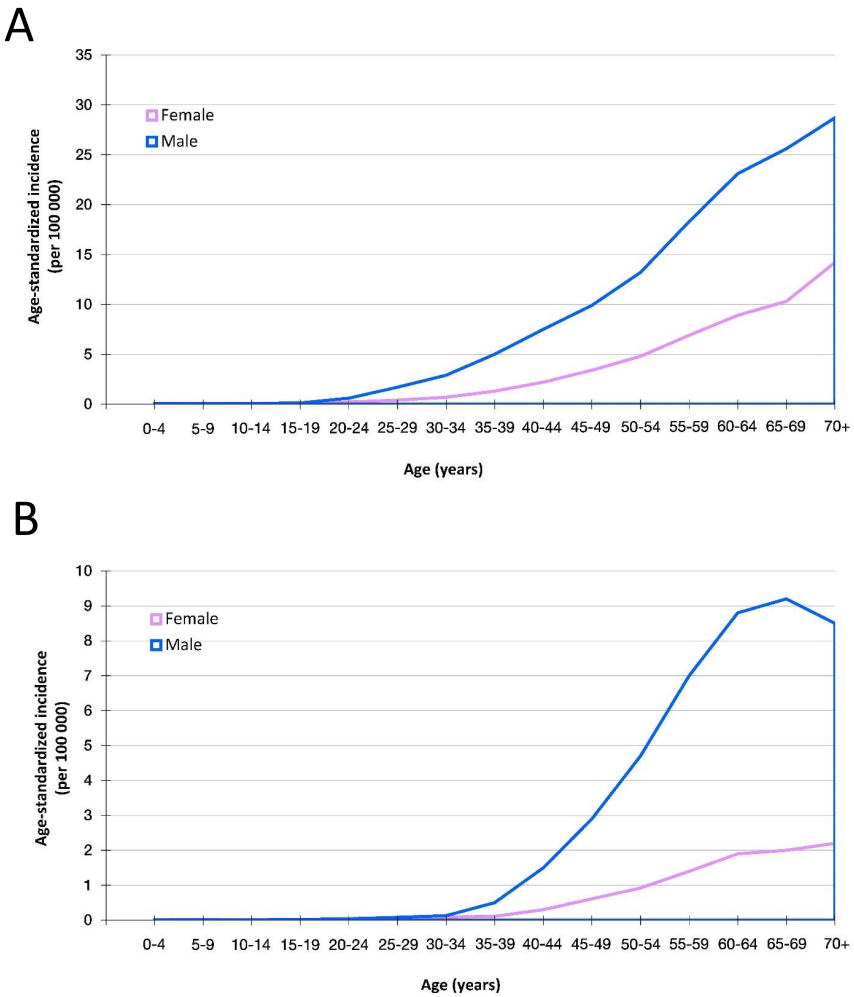
In 2020, the incidence rates of oropharyngeal cancer were highest in Europe. The rates (ASIR, per 100 000, in both sexes) were highest in Denmark (5.0), France (4.3), and Romania (4.3). For oropharyngeal cancer mortality, the rates (ASMR, per 100 000, in both sexes) were highest in Slovakia (2.5), followed by the Republic of Moldova (2.3) and Romania (2.3) (Ferlay et al., 2020).

(c) Socioeconomic status

For oral cancer (including lip cancer), the ASIR and ASMR were highest in countries with medium levels of the Human Development Index (HDI); for oropharyngeal cancer, the ASIR was highest in countries with very high HDI, and the ASMR was highest in countries with medium HDI (Ferlay et al., 2020) (Fig. 1.5). HDI was found to be negatively associated with the annual percentage change in the ASIR and ASMR for oral cancer (Ren et al., 2020).

A meta-analysis of 41 case–control studies revealed that low socioeconomic status increased the risk of oral cancer (pooled adjusted odds

Fig. 1.3 Age-specific incidence curves in the world population for oral cancer (A) and oropharyngeal cancer (B), 2020



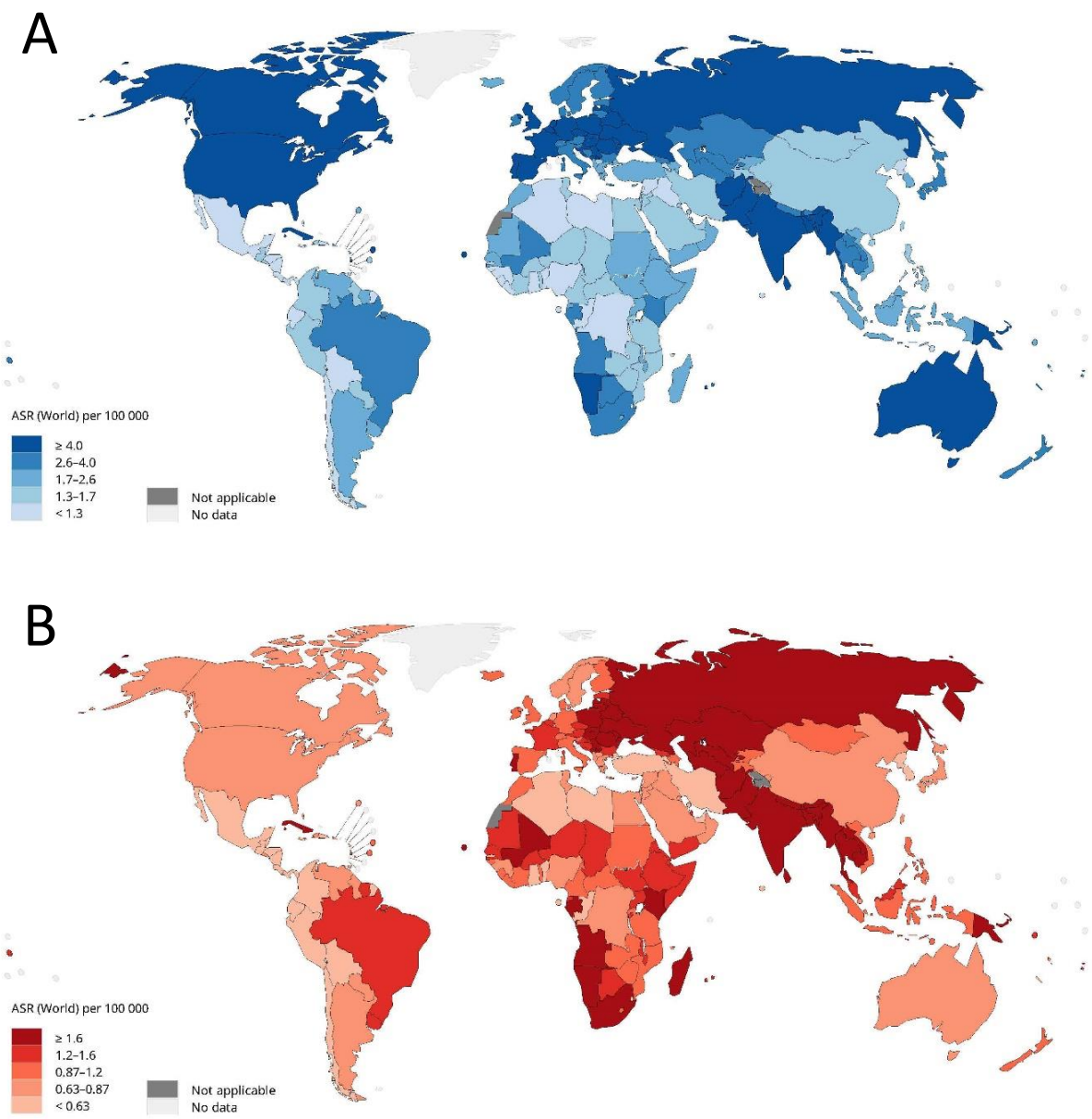
From Ferlay et al. (2020).

ratio [OR], 3.41; 95% confidence interval [CI], 2.14–5.44; n = 2), as did low occupational social class (pooled adjusted OR, 1.41; 95% CI, 1.10–1.79; n = 4) and low educational attainment (pooled adjusted OR, 1.74; 95% CI, 1.33–2.27; n = 17) (Conway et al., 2008). A large pooled analysis by the International Head and Neck Cancer Epidemiology (INHANCE) consortium found an association between low educational attainment and increased risk of oral cancer (OR, 1.33; 95% CI, 1.02–1.75) and oropharyngeal cancer (OR, 1.88; 95% CI, 1.23–2.88), independent of age, sex, centre, cigarette smoking, and alcohol consumption (Conway et al., 2015).

(d) Time trends in incidence

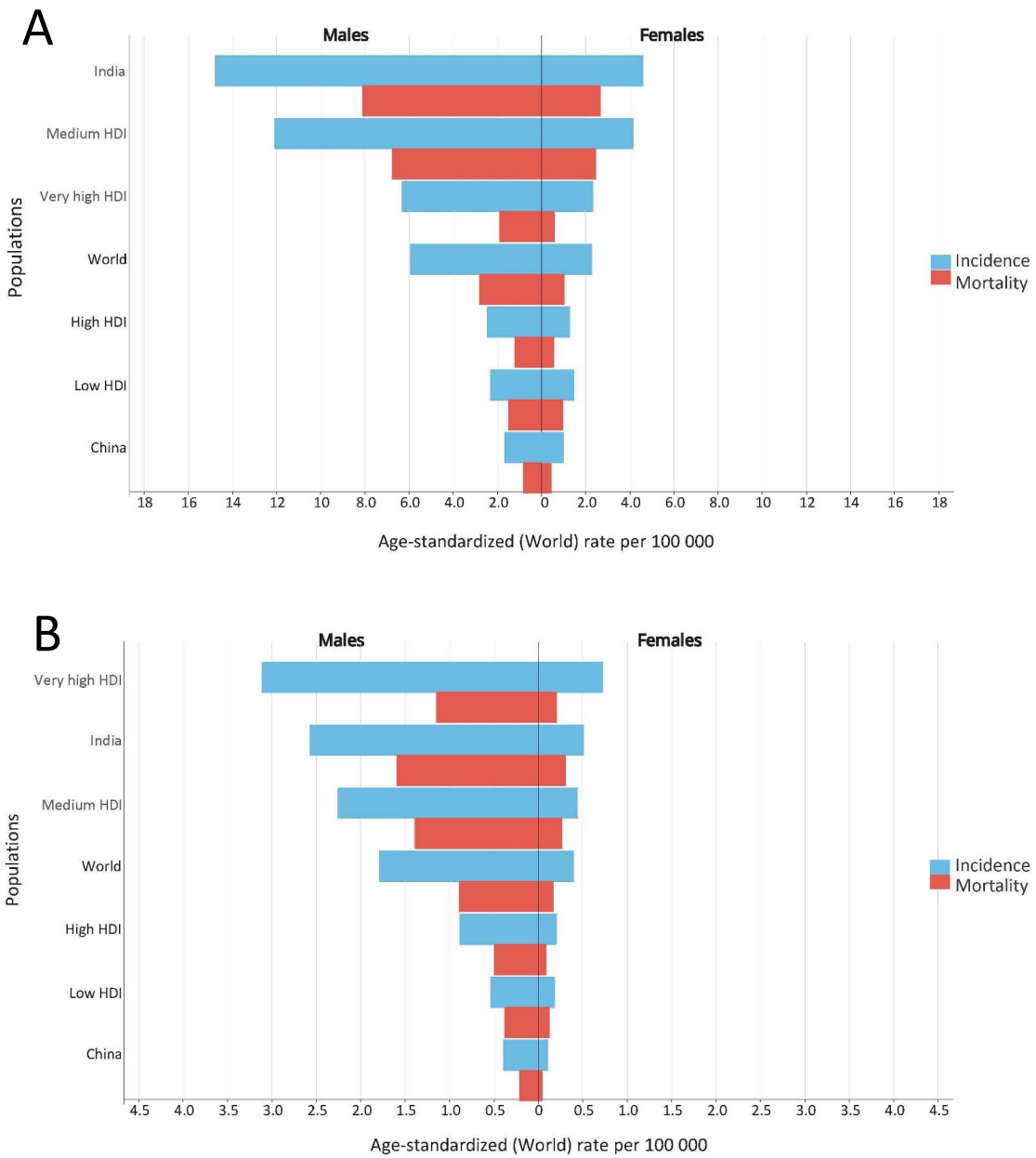
During the past two decades, incidence rates of oral and oropharyngeal cancers combined have decreased in several countries in North America, South-East Asia, and Europe, especially in males. However, in females, incidence rates have increased mainly in the European countries, and in males, incidence rates have increased in the United Kingdom, Japan, and

Fig. 1.4 Global distribution of estimated age-standardized (World) incidence rates (A) and mortality rates (B) per 100 000 for oral cancer in both sexes, 2020



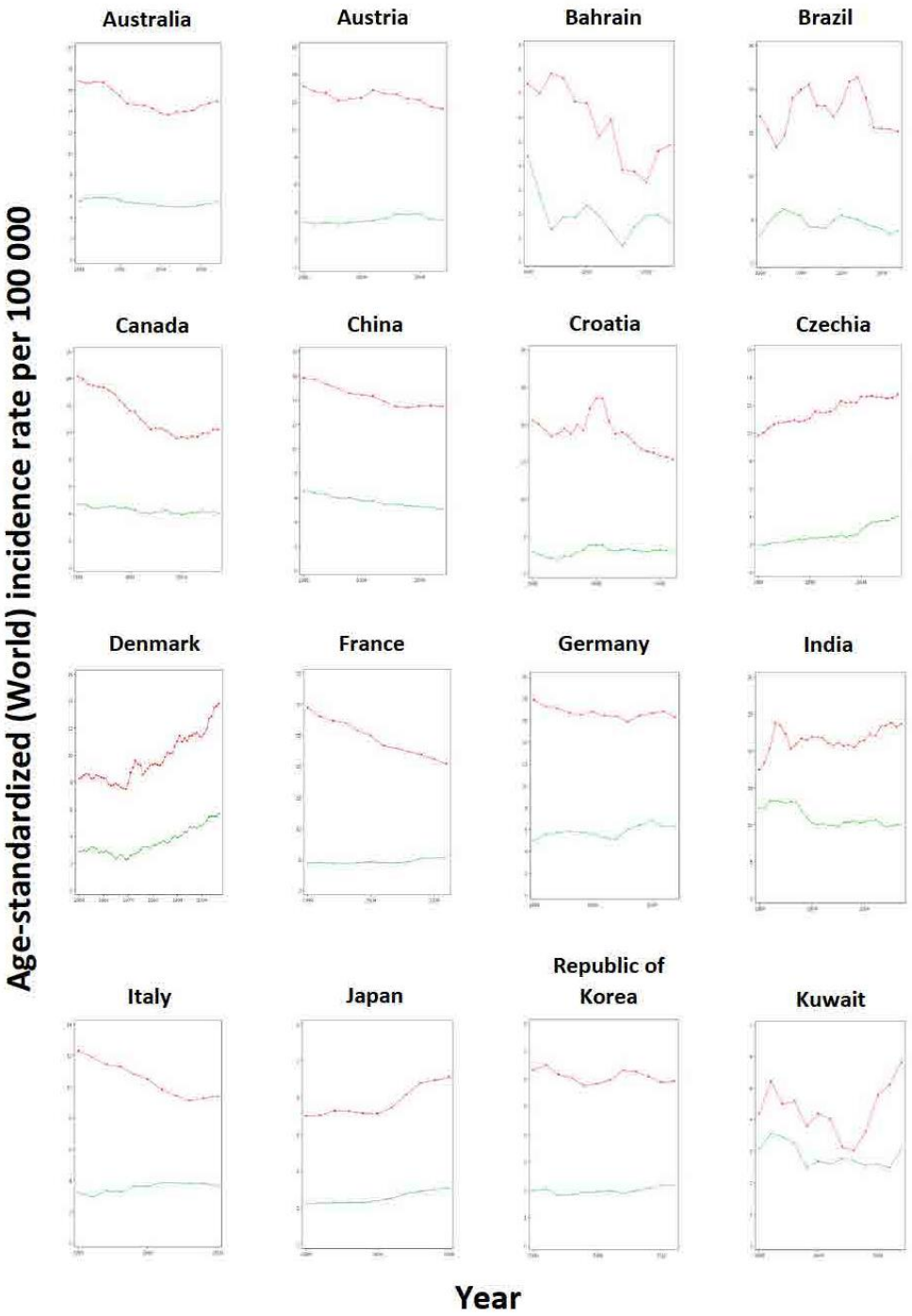
From Ferlay et al. (2020).

Fig. 1.5 Estimated age-standardized (World) incidence and mortality rates per 100 000 for oral cancer (A) and oropharyngeal cancer (B), by Human Development Index (HDI) level, 2020



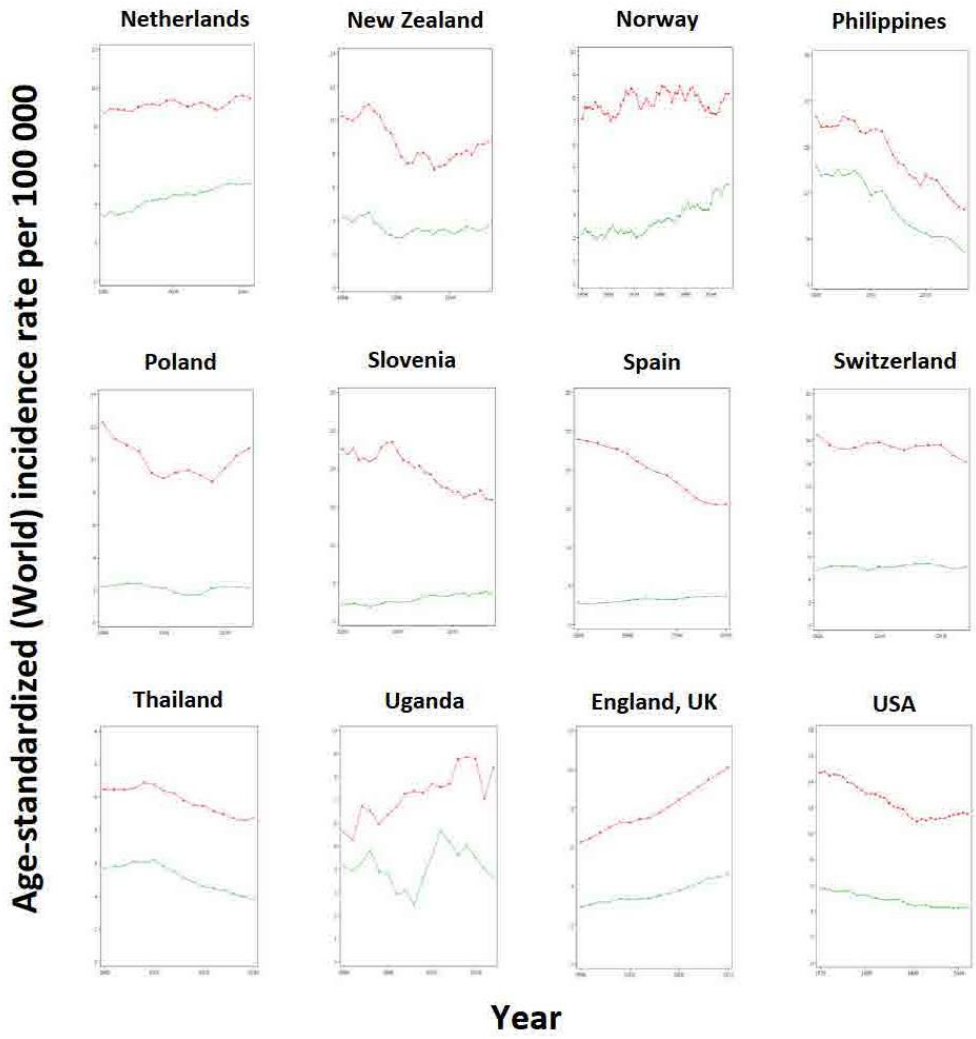
From Ferlay et al. (2020).

Fig. 1.6 Time trends in age-standardized (World) incidence rates per 100 000 for oral cancer and oropharyngeal cancer combined, by country, in males (red) and females (green)



From Ferlay et al. (2020).

Fig. 1.6 (continued)



From Ferlay et al. (2020).

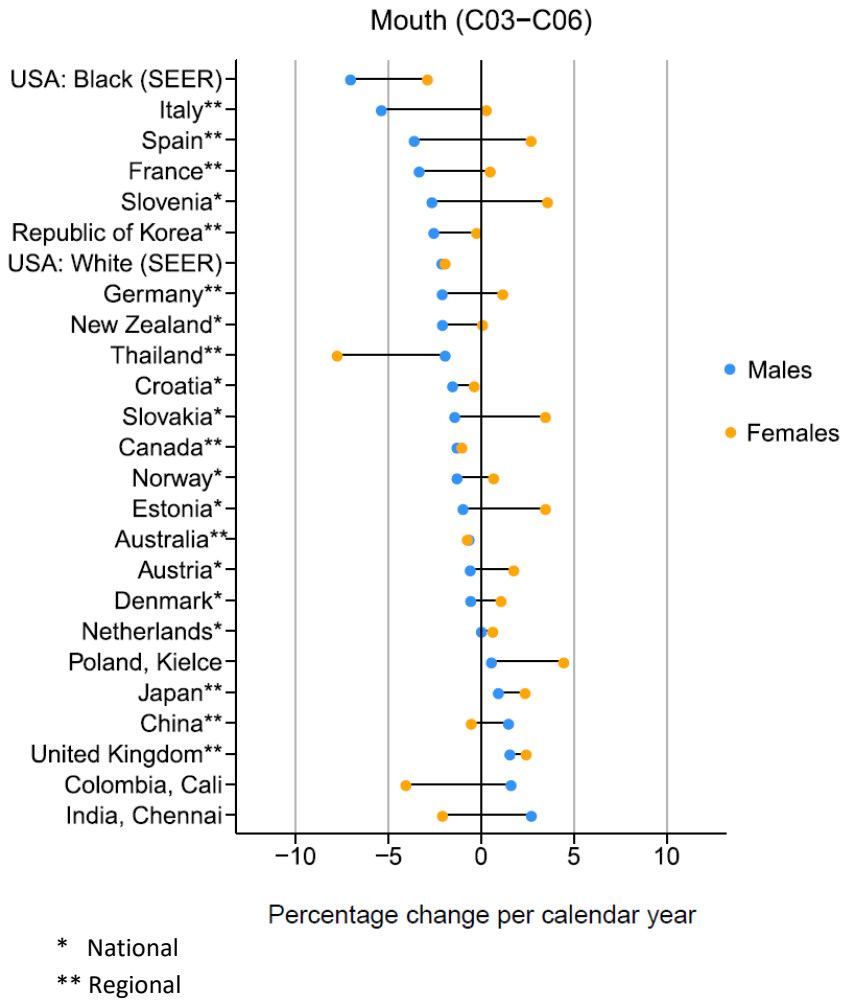
Czechia (Fig. 1.6; Bosetti et al., 2020; Ferlay et al., 2020; Lin, 2020). Incidence rates of oropharyngeal cancer specifically have increased in several countries in the Americas, Europe, and Asia, especially in males (Bosetti et al., 2020; Menezes et al., 2021).

In most countries, incidence rates of cancer of the oral cavity (excluding the lip and the tongue) have decreased more in males than in females. In females, incidence rates have decreased in Thailand, Colombia, and India (Fig. 1.7; Miranda-Filho and Bray, 2020). Incidence rates of tongue cancer have increased in the USA and Thailand (Argirion et al., 2019; Kim and Kim, 2020).

(e) Projections of incidence and mortality

Table 1.1 shows estimates of the incidence and mortality for oral cancer and oropharyngeal cancer in 2020 and projected to 2040, by HDI category and overall. Globally, the projected increase from 2020 to 2040 in the estimated

Fig. 1.7 Estimated annual percentage change (EAPC) of the trends in age-standardized rates of mouth cancer in selected registry populations by sex, in 1998–2012, sorted in descending order according to EAPC in men



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number of new cases per year is 49.6% for oral cancer and 40.2% for oropharyngeal cancer. For both oral cancer and oropharyngeal cancer, the highest increases by 2040 in the numbers of new cases and deaths are expected to occur in countries with low HDI (Table 1.1) (Ferlay et al., 2020).

(f) Lip cancer

Incidence rates of lip cancer are relatively high in certain parts of the world as a result of excessive exposure to ultraviolet radiation from sunlight. The incidence rates are highest in Australia in both sexes, followed by Spain and Poland in males and the Netherlands and Norway in females (Fig. 1.8A). Although incidence rates of lip cancer have decreased in most countries, incidence rates have increased in females in Germany, the Netherlands, Norway, China, Slovakia, and Japan and in males in India (Fig. 1.8B; Miranda-Filho and Bray, 2020).

Table 1.1 Global burden of oral cancer and oropharyngeal 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 (millions)	Number of new cases		Increase (%)	Number of deaths		Increase (%)
		2020	2040		2020	2040	
Oral cancer							
Very high HDI	1 564	118 036	147 172	24.7	37 048	48 590	31.2
High HDI	2 909	72 418	112 182	54.9	34 765	57 958	66.7
Medium HDI	2 327	177 018	285 228	61.1	99 662	161 437	62.0
Low HDI	990	10 126	20 163	99.1	6 251	12 554	100.8
World	7 791	377 598	564 745	49.6	177 726	280 539	57.8
Oropharyngeal cancer							
Very high HDI	1 564	47 971	56 233	17.2	18 592	23 522	26.5
High HDI	1 564	20 614	30 097	46.0	11 248	17 532	55.9
Medium HDI	2 327	27 932	47 869	71.4	17 053	29 241	71.5
Low HDI	990	1 839	3 727	102.7	1 230	2 510	104.1
World	7 791	98 356	137 926	40.2	48 123	72 805	51.3

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).

1.2.2 Oral potentially malignant disorders

An oral potentially malignant disorder (OPMD) is defined as any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer (Warnakulasuriya et al., 2007). OPMDs share common risk factors with invasive carcinoma of the oral cavity. OPMDs include leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus, actinic keratosis (actinic cheilitis), palatal lesion in reverse smokers (in reverse smoking, the smoker places the lit end of the cigarette, rather than the unlit end, into their mouth and inhales the smoke), oral lupus erythematosus, dyskeratosis congenita, oral lichenoid lesion, and oral graft-versus-host disease (Warnakulasuriya and Greenspan, 2020).

The overall global prevalence of OPMDs is 4.47% (95% CI, 2.43–7.08%), with geographical variations; the highest prevalence is observed in Asia (10.54%; 95% CI, 4.60–18.55%), followed by South America and the Caribbean (3.93%; 95% CI, 2.43–5.77%), the Middle East (3.72%; 95% CI, 2.91–4.67%), and Europe (3.07%; 95% CI, 1.64–4.93%) (Mello et al., 2018).

Globally, the highest prevalence is observed for oral submucous fibrosis (4.96%; 95% CI, 2.28–8.62%). Other common OPMDs include leukoplakia (4.11%; 95% CI, 1.98–6.97%), actinic cheilitis (2.08%; 95% CI, 0.94–3.67%), erythroplakia (0.17%; 95% CI, 0.07–0.32%) (Mello et al., 2018), and oral lichen planus (1.01%; 95% CI, 0.74–1.32%) (González-Moles et al., 2021).

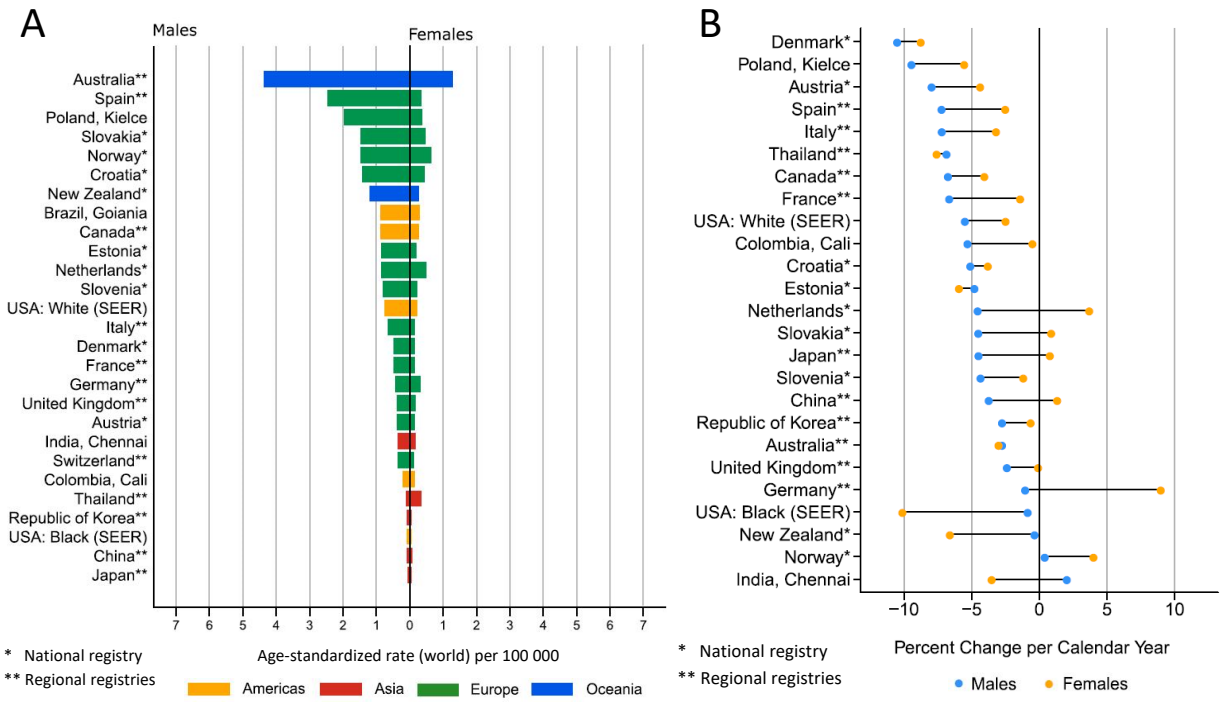
1.3 Oral neoplasia

1.3.1 Classification and natural history of OPMDs and oral cancer

Oral cancer includes cancers of the lip, other and unspecified parts of the tongue (excluding the lingual tonsils), gum, floor of the mouth, palate, and other and unspecified parts of the mouth (Conway et al., 2018).

The term OPMD was introduced in 2005, replacing the terms "oral precancerous/premalignant lesions and conditions" (Warnakulasuriya

Fig. 1.8 (A) Bar chart of age-standardized incidence rates of lip cancer in selected countries, by sex, all ages, in 2008–2012. (B) Estimated annual percentage change (EAPC) of the trends in age-standardized rates of lip cancer in selected registry populations by sex, in 1998–2012, sorted in descending order according to EAPC in men



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et al., 2007). OPMDs comprise a wide range of disorders (Box 1.1) with varying rates of malignant transformation into oral cancer, of which oral squamous cell carcinoma (OSCC) is the most common type (Holmstrup et al., 2006; Speight et al., 2018; Farah et al., 2019). In 2020, the World Health Organization (WHO) Collaborating Centre for Oral Cancer recommended a list of OPMDs, which include leukoplakia, proliferative verrucous leukoplakia (PVL), erythroplakia, oral submucous fibrosis, oral lichen planus (OLP), actinic keratosis (actinic cheilitis), nicotinic stomatitis in reverse smokers, oral lupus erythematosus, and dyskeratosis congenita. Oral lichenoid lesion and oral graft-versus-host disease were added to the list on the basis of the available evidence on their malignant potential (de Araújo et al., 2014; González-Moles et al., 2019; Warnakulasuriya and Greenspan, 2020). The diagnosis of an OPMD significantly increases the risk of developing oral cancer during a lifetime (Warnakulasuriya et al., 2007; Reibel et al., 2017; Speight et al., 2018; Warnakulasuriya and Greenspan, 2020).

(a) Clinical presentation of OPMDs

Leukoplakia is a predominantly white plaque of questionable risk having excluded other known diseases that carry no increased risk of cancer (Warnakulasuriya et al., 2007). This OPMD has a wide range of clinical appearances, ranging from homogeneous to non-homogeneous, including nodular leukoplakia, verrucous leukoplakia, and erythroleukoplakia

Box 1.1 Classified oral potentially malignant disorders (OPMDs)

Erythroplakia
Erythroleukoplakia
Leukoplakia
Proliferative verrucous leukoplakia
Oral submucous fibrosis
Palatal lesion associated with reverse smoking
Oral lichenoid lesion[a]
Oral lichen planus
Actinic keratosis (actinic cheilitis)
Smokeless tobacco keratosis[b]
Oral graft-versus-host disease
Oral lupus erythematosus
Familial cancer syndromes including Fanconi anaemia, dyskeratosis congenita, xeroderma pigmentosum, Li–Fraumeni syndrome, Bloom syndrome, ataxia–telangiectasia, and Cowden syndrome

[a] Oral lesion resembling lichen planus but lacking typical clinical or histopathological appearances.
[b] Risk varies with tobacco type.
Adapted from WHO Classification of Tumours Editorial Board (2023).

(Warnakulasuriya and Greenspan, 2020). Several other white lesions should be excluded to arrive at the clinical diagnosis of leukoplakia, such as white sponge naevus, acute pseudomembranous candidiasis, frictional keratosis, OLP, chronic hyperplastic candidiasis, leukoedema, chemical injury, uremic stomatitis, nicotinic stomatitis, skin grafts, and oral hairy leukoplakia (Warnakulasuriya, 2018).

Proliferative verrucous leukoplakia presents as multiple white patches at different sites in the oral cavity (usually on the gingiva, palate, and alveolar mucosa), with a preponderance in elderly women. PVLs start as flat lesions, and most of them progress to a verrucous appearance. In the early stages, PVL may mimic OLP clinically and histologically (McParland and Warnakulasuriya, 2021; Thompson et al., 2021).

Erythroplakia is a predominantly fiery red patch that cannot be characterized clinically or pathologically as any other definable disease (Warnakulasuriya et al., 2007). Other definable red lesions should be excluded to arrive at the clinical diagnosis of erythroplakia, such as erythematous candidiasis, inflammatory conditions, denture-induced stomatitis, erythema migrans, desquamative gingivitis, erosive OLP, oral lupus erythematosus, and vesiculobullous disorders (Reichart and Philipsen, 2005).

Most lesions of *oral lichen planus* present as white striae (reticular or annular) or plaques; some have papular, atrophic, erosive, bullous, or ulcerative features. The lesions are usually present bilaterally (Warnakulasuriya and Greenspan, 2020). Incipient PVL often mimics OLP lesions both clinically and histologically (Gilligan et al., 2021); this leads to diagnostic challenges.

Common signs and symptoms of *oral submucous fibrosis* are a burning sensation when eating spicy food, diffuse blanching of oral mucosa, and restricted mouth opening. In addition, restriction in tongue movement, palpable fibrous bands, a leathery feeling of the mucosa, depapillation of the tongue, shrunken uvula, and sunken cheeks are present to various degrees (Tilakaratne et al., 2006).

(b) Histopathological spectrum of OPMDs

Histopathological features vary depending on the type of OPMD. However, the presence of variable levels of epithelial dysplasia is the most

important histopathological feature common to all OPMDs, and this is a fairly reliable biological marker, which guides treatment stratification based on the risk of malignant transformation. Epithelial dysplasia in the oral mucosa is graded into three categories: mild, moderate, and severe. Grading of epithelial dysplasia using this scale is subjective and leads to significant intra-examiner and inter-examiner variability (Tilakaratne et al., 2019). In 2017, the fourth edition of the WHO Classification of Head and Neck Tumours introduced a new binary grading system: low-risk and high-risk epithelial dysplasia (Reibel et al., 2017).

The histopathological spectrum of leukoplakias varies from cases of keratosis without dysplasia to mild, moderate, or severe dysplasia. Erythroplakia is a high-risk lesion because most cases at diagnosis are either severe epithelial dysplasia or in situ OSCC. PVL is a lesion with minimal dysplasia, although about 50% of PVLs transform into OSCC. Early cases of PVL have histopathological features similar to those of OLP, which may lead to misdiagnosis (Thompson et al., 2021). OLP has orthokeratinized or parakeratinized surface epithelium with a band-like lymphocytic infiltrate in the upper corium and associated basal cell destruction and apoptosis. Epithelial dysplasia may be present in a minority of OLP lesions, and this feature increases the risk of malignant transformation. Oral submucous fibrosis has characteristic histopathological features, such as atrophy of the surface epithelium and hyalinization and fibrosis of the submucosa, which extend deep into the underlying connective tissue and muscle as the disease progresses. Atrophic surface epithelium may have features of epithelial dysplasia in some cases (Utsunomiya et al., 2005).

(c) Malignant transformation of OPMDs

OPMDs are a heterogeneous group of lesions, and the rates of transformation to cancer vary from 1.4% to 49.5% (Iocca et al., 2020). Rates of malignant transformation of OPMDs vary substantially depending on the study population, risk habits, and site in the oral cavity, and from study to study (Reibel, 2003; Bouquot et al., 2006; Napier and Speight, 2008).

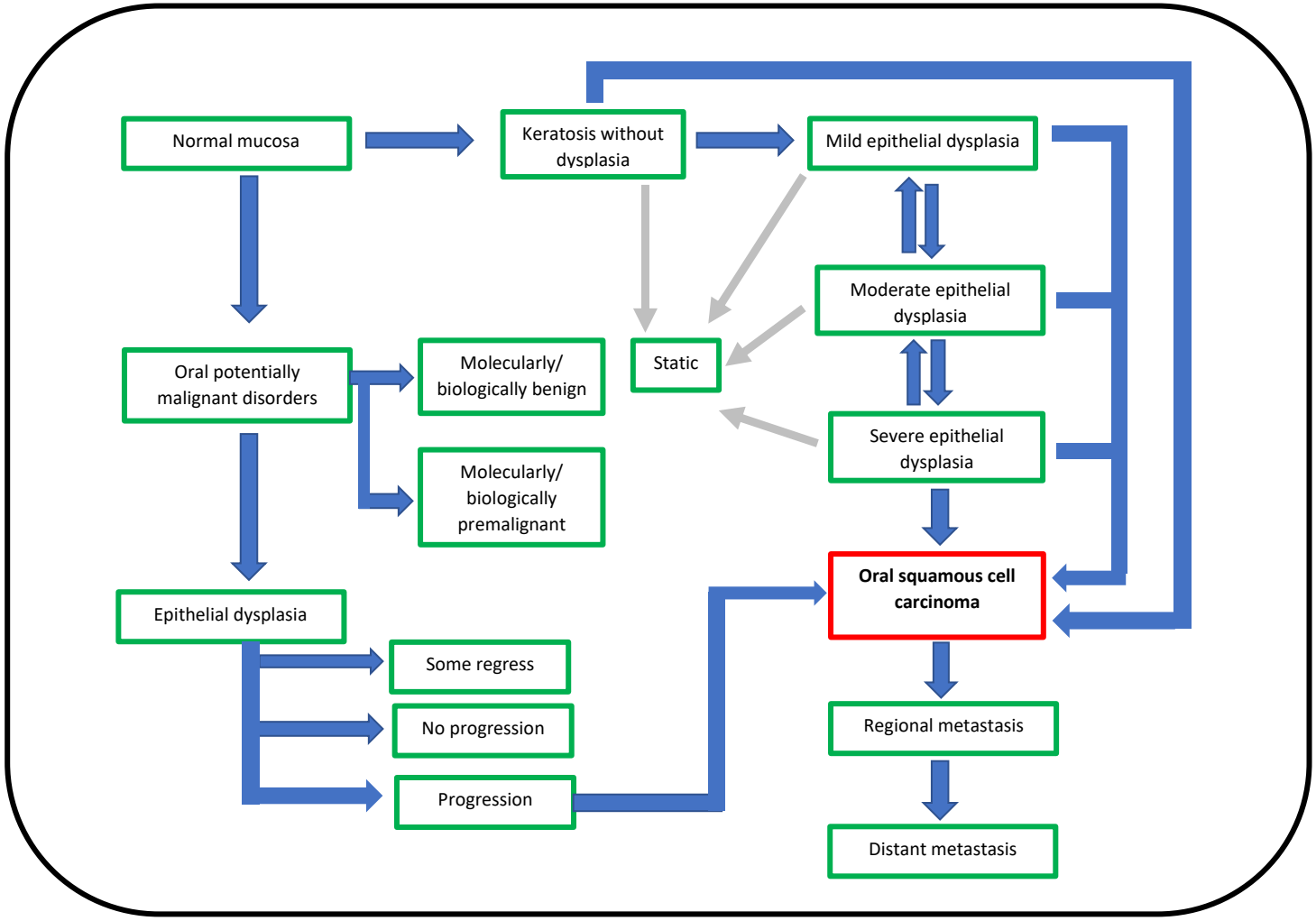
PVL and erythroplakia have the highest malignant transformation rates (30–50%), and OLP has the lowest (~1–2%) (Warnakulasuriya and Greenspan, 2020). The risk of transformation of leukoplakia depends on the clinical type and grade of epithelial dysplasia (Mehanna et al., 2009). Globally, the malignant transformation rate for leukoplakia was reported as 1.36% per year (95% CI, 0.69–2.03%) by Petti (2003) and as 9.8% (95% CI, 7.9–11.7%) in the systematic review and meta-analysis by Aguirre-Urizar et al. (2021) based on 5-year data. The natural history of leukoplakia is a dynamic rather than a static process with respect to malignant transformation. The malignant transformation rates of oral submucous fibrosis vary widely across studies, ranging from 7% to 13% (Tilakaratne et al., 2006; Ekanayaka and Tilakaratne, 2016).

Over time, OPMDs may persist unchanged, increase in size, regress in size, or even completely resolve (Fig. 1.9), which has been shown in many follow-up studies (Mehta et al., 1972; Gupta et al., 1980; Silverman et al., 1984; Holmstrup et al., 2006; Speight et al., 2018; Farah et al., 2019). Even in the absence of significant epithelial dysplasia, some OPMDs can progress to OSCC with time; therefore, lifetime clinical follow-up is highly recommended (Villa et al., 2019).

(d) Clinical features of oral cancer

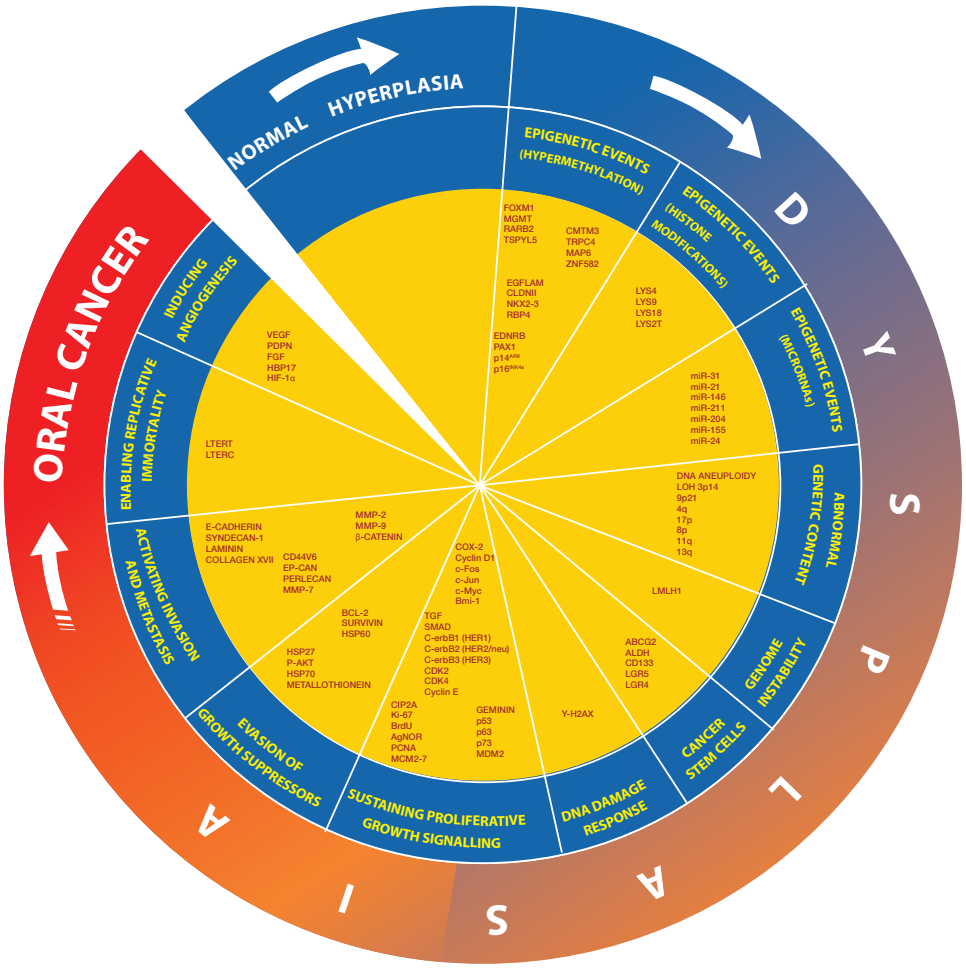
The clinical features of oral cancer vary depending on the site and the stage of clinical presentation (Bagan et al., 2010; Dissanayaka et al., 2012). The two most common sites for oral cancer are the tongue and the buccal mucosa. Other sites of involvement are the floor of the mouth, the gingivae, and the palate (Warnakulasuriya, 2009). The lesions have a variable size, ranging in diameter from a few

Fig. 1.9 Natural history of oral potentially malignant disorders and oral cancer



Created by the Working Group.

Fig. 1.10 Molecular events in the natural history of oral cancer



LOH, loss of heterozygosity.
Created by the Working Group.

millimetres to several centimetres in advanced cases.

In the initial stages, oral malignant lesions present as well-demarcated erythroleukoplakic lesions consisting of red, white, or red and white areas with a slight roughness along with reduced elasticity or induration of the soft tissue. As the disease advances, there is ulceration and/or nodularity and fixation to underlying tissues. The tumours can be either exophytic or endophytic, and many of them may have residual red and white areas or a nodular and/or granular appearance, indicating their possible origin from an OPMD. The base of ulcerated tumours is indurated, and the surrounding mucosa has everted margins because of proliferation of the epithelium. Early cancers are asymptomatic, but advanced tumours can be very painful. Tongue cancer causes difficulty in swallowing and speaking, and restricted movements. Cancer of the buccal mucosa can lead to severe trismus when it has invaded into muscles. Enlarged and fixed cervical lymph nodes due to locoregional spread is a late presentation of the disease (Bagan et al., 2010).

(e) Histopathology of oral cancer

The histopathological hallmark of OSCC is the invasion of malignant epithelial cells into the underlying connective tissue. When the tumour cells resemble the surface normal squamous epithelium, with marked keratin formation, the cancer is categorized as well-differentiated OSCC. At the other end of the spectrum, when the tumour cells do not bear any resemblance to the squamous cells and there is no evidence of keratin formation, the cancer is categorized as poorly differentiated OSCC. The tumours in between these two extremes are categorized as moderately differentiated OSCC. In addition to the conventional types, some subtypes of OSCC have also been described; these include basaloid, adenoid (acantholytic), adenosquamous, papillary, spindle cell, cuniculatum, and verrucous carcinoma.

Histopathological parameters that must be contained in a pathology report include the level of differentiation, vascular and perineural invasion, pattern of invasion, depth of invasion, and immune response. In addition, the clearance distance of excision margins and lymph node status should be included in a report of surgical excision of the primary tumour with neck dissection (i.e. removal of the lymph nodes in the neck). Numerous molecular events have been described with respect to oral carcinogenesis (Dionne et al., 2015; Nikitakis et al., 2018; Farah, 2021; Fig. 1.10).

(f) Prognosis of oral cancer

Prognosis of oral cancer depends on multiple factors, including tumour-, host-, and treatment-related factors. The most significant prognostic factors are the stage of disease, depth of invasion, pattern of invasion, lymphovascular invasion, nodal status, and distant metastases (Dissanayaka et al., 2012; De Silva et al., 2018). The stage at diagnosis and the mortality rate vary according to the primary site of the tumour; for example, cancer of the lower lip is often diagnosed at an early stage, and the highest mortality rate is reported in patients with tongue cancer (Su et al., 2019). Positive regional lymph nodes, particularly with extracapsular spread, have a direct negative effect on prognosis (Abdel-Halim et al., 2021). Although the 5-year survival rate of OSCC is reported to be about 50%, recent data show an improvement to 66% in some centres (Liu et al., 2021).

1.3.2 Stage at diagnosis and stage-related survival

Prognosis of cancers of the lip, oral cavity, and oropharynx depends mainly on the stage of the disease at diagnosis. Table 1.2 shows survival rates for these cancer types by country or territory in five continents in 2006–2014 (IARC, 2022). Heterogeneity across countries is high; 5-year survival rates range from 0% to 64% (median, 39%) for patients with cancer of the lip or oral cavity and from 0% to 67% (median, 32%) for patients with oropharyngeal cancer.

The extent of the disease can be classified as localized (tumours confined to the organ of origin without invasion into the surrounding tissue or organs and without involvement of any regional or distant lymph nodes or organs), regional (tumours invading the surrounding tissue or organs, with or without the involvement of the regional lymph nodes, but not involving non-regional lymph nodes or organs), or with distant metastasis (spreading to the non-regional lymph nodes or distant organs; or unknown) (WHO Classification of Tumours Editorial Board, 2023). Overall, cancer of the lip or oral cavity is more frequently diagnosed with localized stage, compared with oropharyngeal cancer, which is more frequently diagnosed with regional disease. [Limitations of the study are significant, including a high proportion of unclassified cancers (~10% to 50%) and the variability in the number of patients analysed per country, which

Table 1.2 Survival (at 1 year, 3 years, and 5 years) of oral cancer and oropharyngeal cancer, by country or territory in 2006–2014, for both sexes combined

Country or territory	Survival (%)					
	Oral cancer			Oropharyngeal cancer		
	1 year	3 years	5 years	1 year	3 years	5 years
Algeria	94	31	0	50	0	0
Argentina	62	42	35	57	38	34
Bahrain	71	52	52	75	75	38
Brazil	77	55	49	58	39	31
Chile	61	43	34	52	36	29
China	72	53	47	54	35	30
Colombia	56	39	39	50	0	0
Costa Rica	73	57	52	67	49	42
Ecuador	65	50	45	80	46	31
India	71	47	40	61	32	24
Israel	82	66	58	85	63	55
Republic of Korea	80	62	57	81	65	58
Malaysia	58	36	31	68	53	47
Martinique, France	65	45	39	71	41	41
Peru	65	45	37	72	57	44
Puerto Rico, USA	65	27	16	60	27	15
Saudi Arabia	81	64	64	100	67	67
Seychelles	45	29	19	N/A	N/A	N/A
South Africa	49	29	18	44	31	31
Thailand	51	32	26	49	28	23
Turkey	83	68	59	74	51	40
Uruguay	60	37	31	56	38	32

N/A, not available.
Compiled from IARC (2022).

is very small in some cases (ranging from 13 to 3453).]

The Surveillance, Epidemiology, and End Results (SEER) database tracks 5-year relative survival rates for oral cancer and oropharyngeal cancer in the USA. In patients with oral cancer, based on different anatomical subsites (lip, tongue, or floor of the mouth), the 5-year relative survival rates were 73–94%, 42–70%, and 23–41% for localized, regional, and distant disease, respectively; survival was worse for patients with cancer of the floor of the mouth than for those with tongue cancer. In patients with oropharyngeal cancer, the 5-year relative survival rates were 59%, 62%, and 29% for localized, regional, and distant disease, respectively (American Cancer Society, 2023).

The treatment of cancer of the lip, oral cavity, and oropharynx is driven mainly by staging of the disease. Since its conception in 1959, the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) tumour–node–metastasis (TNM) staging system has become the main modality of tumour staging and is used to tailor the treatment of patients (Tirelli et al., 2018a). New editions of the AJCC TNM staging system are regularly published to improve the ability to predict patient outcomes. The eighth edition, which was published in 2017 (AJCC, 2017), had two major changes in TNM

Table 1.3 Tumour–node–metastasis staging system for carcinomas of the oral cavity

Primary tumour (T)		Clinical N (cN)		Pathological N (pN)		Distant metastasis (M)	
T category	**T criteria[a]**	**N category[b]**	**N criteria**	**N category[b]**	**N criteria**	**M category**	**M criteria**
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma in situ	N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE(–)	N1	Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE(–)		
T1	Tumour ≤ 2 cm with DOI ≤ 5 mm	N2	Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm in greatest dimension and ENE(–); **or** Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–); **or** Metastases in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–)	N2	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension and ENE(+); **or** Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm in greatest dimension and ENE(–); **or** Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–); **or** Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension, and ENE(–)		
T2	Tumour ≤ 2 cm, with DOI > 5 mm and ≤ 10 mm; **or** Tumour > 2 cm and ≤ 4 cm, with DOI ≤ 10 mm	N2a	Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm in greatest dimension and ENE(–)	N2a	Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension and ENE(+); **or** Metastasis in a single ipsilateral lymph node > 3 cm and ≤ 6 cm in greatest dimension and ENE(–)		
T3	Tumour > 2 cm and ≤ 4 cm with DOI > 10 mm; **or** Tumour > 4 cm with DOI ≤ 10 mm	N2b	Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–)	N2b	Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–)		

Table 1.3 (continued)

Primary tumour (T)		Clinical N (cN)		Pathological N (pN)		Distant metastasis (M)	
T category	**T criteria[a]**	**N category[b]**	**N criteria**	**N category[b]**	**N criteria**	**M category**	**M criteria**
T4	Moderately advanced or very advanced local disease	N2c	Metastases in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension, and ENE(–)	N2c	Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension, and ENE(–)		
T4a	Moderately advanced local disease Tumour > 4 cm with DOI > 10 mm; **or** Tumour invades adjacent structures only (e.g. through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face) Note: Superficial erosion of bone/ tooth socket (alone) by a gingival primary is not sufficient to classify a tumour as T4.	N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(–); **or** Metastasis in any lymph node(s) and clinically overt ENE(+)	N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(–); **or** Metastasis in a single ipsilateral lymph node > 3 cm in greatest dimension and ENE(+); **or** Metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, any ENE(+); **or** Metastasis in a single contralateral lymph node of any size and ENE(+)		
T4b	Very advanced local disease Tumour invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery	N3a	Metastasis in a lymph node > 6 cm in greatest dimension, and ENE(–)	N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE(–)		

Table 1.3 (continued)

Primary tumour (T)		Clinical N (cN)		Pathological N (pN)		Distant metastasis (M)	
T category	**T criteria[a]**	**N category[b]**	**N criteria**	**N category[b]**	**N criteria**	**M category**	**M criteria**
T4b (cont.)		N3b	Metastasis in any lymph node(s) and clinically overt[c] ENE(+)	N3b	Metastasis in a single ipsilateral lymph node > 3 cm in greatest dimension and ENE(+); **or** Metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, any ENE(+); **or** Metastasis in a single contralateral lymph node of any size and ENE(+)		

AJCC, American Joint Committee on Cancer; DOI, depth of invasion; ENE, extranodal extension; TNM, tumour–node–metastasis.

[a] DOI is depth of invasion and **not** tumour thickness.

[b] A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).

[c] The presence of skin involvement or soft tissue invasion with deep fixation or tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical ENE.

Adapted from AJCC (2017). The original source for this information is the AJCC cancer staging manual, 8th edition, published by Springer International Publishing. Corrected at 4th printing, 2018.

Table 1.4 Tumour–node–metastasis staging system for carcinomas of the oral cavity: prognostic stage groups

T category	N category	M category	Stage group
Tis	N0	M0	Stage 0
T1	N0	M0	Stage I
T2	N0	M0	Stage II
T3	N0	M0	Stage III
T1, T2, T3	N1	M0	Stage III
T4a	N0, N1	M0	Stage IVA
T1, T2, T3, T4a	N2	M0	Stage IVA
Any T	N3	M0	Stage IVB
T4b	Any N	M0	Stage IVB
Any T	Any N	M1	Stage IVC

Adapted from AJCC (2017). The original source for this information is the AJCC cancer staging manual, 8th edition, published by Springer International Publishing. Corrected at 4th printing, 2018.

categorization compared with previous editions (Amin et al., 2017) (Table 1.3 and Table 1.4): inclusion of the depth of invasion (DOI) of the tumour (≤ 5 mm, 5–10 mm, and > 10 mm) affects the T categorization, and inclusion of the extranodal extension (ENE) affects the N categorization. The T1–3 but not the T4 classification is dependent on both the size of the tumour and the DOI. Also, extrinsic muscle involvement has been excluded as a criterion for T4 staging of tongue cancer. Finally, the absence of ENE is a prerequisite to classify N stage as N1, N2, or N3a disease, except if there is ENE of less than 3 cm in diameter in a single node (pN2a) (Zanoni and Patel, 2020).

Based on data from the United States National Cancer Database and staging with the eighth edition of the TNM staging system, the 5-year overall survival rate of patients with oral cancer who received treatment was 78.8% (median survival not reached) for stage 0, 72.2% (median survival not reached) for stage I, 57.5% (median survival, 5.70 years) for stage II, 55.1% (median survival, 5.59 years) for stage III, 39.7% (median survival, 3.08 years) for stage IVA, 27.1% (median survival, 1.45 years) for stage IVB, and 15.8% (median survival, 1.27 years) for stage IVC (Cramer et al., 2018).

Besides disease staging, many other factors may affect the prognosis of individual patients: access to specialized care, associated comorbidities, and the quality of treatment planning, which is multidisciplinary in nature and is strongly linked to the experience of the team (Hansen et al., 2020). Finally, it is important to note that one quarter to one third of deaths in patients with head and neck squamous cell carcinoma are attributable to a second primary malignancy in the field of cancerization; this may affect the upper aerodigestive tract again, the oesophagus, or the lung, which are among the most frequent anatomical sites (Braakhuis et al., 2002; Baxi et al., 2014).

1.3.3 Treatment and management of OPMDs and oral cancer

(a) Treatment and management of OPMDs

OPMDs are heterogeneous in their clinical presentation. Some OPMDs remain stable for many years or even regress; some eventually transform into oral cancer (see Section 1.3.1). Therefore, one of the main challenges of clinical management is to identify such high-risk lesions (Lingen et al., 2017).

After the clinical diagnosis of an OPMD (Warnakulasuriya et al., 2021), a biopsy is recommended for histopathological diagnosis, which is the current reference standard for confirmation of diagnosis, treatment guidance, and prognostication (Lingen et al., 2017). The histopathological diagnosis of oral epithelial dysplasia, which is routinely classified by grade (mild, moderate, and severe), has both intra-rater and inter-rater variability, which is linked to pathologists' training and experience. Patients with OPMDs that harbour high-grade dysplasia are at a greater risk for development of OSCC than are patients with OPMDs with low-grade dysplasia. Different in vivo optical imaging techniques may reduce diagnostic variability, but they have not been thoroughly evaluated (see Section 4.1.6). Predictive biomarkers, such as loss of heterozygosity (LOH) at specific chromosomal sites and aneuploidy, have been suggested, but none has entered routine clinical use (William et al., 2009; Woo, 2019; Vermorken et al., 2021).

There is no evidence-based international consensus on management algorithms for OPMDs. After diagnosis, the management of OPMDs may include one or more strategies, depending on the grade of dysplasia and other clinical factors. These include preventive strategies (e.g. lifestyle risk modification: cessation of tobacco use and/or alcohol consumption and/or use of areca nut, improvement of diet), disease monitoring or surveillance (i.e. a watchful waiting approach), medical interventions (i.e. use of topical or systemic agents, chemoprevention), surgical management, and others (Warnakulasuriya, 2020; Kerr and Lodi, 2021; Birur et al., 2022). Consensus guidelines for clinical management of patients with OPMDs, focusing on leukoplakia or erythroplakia, oral submucous fibrosis, and OLP, have recently been proposed (Birur et al., 2022). For low-risk lesions, clinical management may be limited to lifelong close surveillance, as an alternative to potentially morbid, repeated, multistep surgical treatments, such as excision or ablation using various techniques, including cold blade or electrocautery, laser, cryotherapy, and photodynamic therapy (Birur et al., 2022). Surgical excision was shown to decrease the rate of malignant transformation of oral dysplasia but not totally eliminate it (Mehanna et al., 2009).

(b) Treatment and management of oral cancer

The different modalities of treatment of oral cancer are surgery, radiotherapy, chemotherapy, and immunotherapy. Treatment planning is done at a multidisciplinary level; the patient is evaluated by a surgeon, a radiation oncologist, and a medical oncologist.

Patients with early-stage and locally advanced oral cancer (stage I and stage II) are typically offered surgical resection. Ipsilateral and sometimes bilateral neck dissection may be recommended. Depending on the depth of invasion and the presence of lymphovascular or perineural invasion, postoperative radiotherapy to the primary site and the neck (unilateral or bilateral) may be recommended.

Management of locoregionally advanced oral cancer (stage III and stage IVA–B) requires multimodality treatment: surgical resection of the primary tumour and neck dissection, followed by postoperative radiotherapy or chemoradiotherapy (Pignon et al., 2000; Shaw et al., 2020). Patients who experience recurrent disease despite these treatments may be candidates for targeted anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies and, more recently, immunotherapy (Bernier, 2016; Vermorken et al., 2021).

Certain adjunct methods used in secondary prevention of oral cancer may also have utility for tertiary prevention. In some studies, autofluorescence and narrow-band imaging (see Section 4.1.3) have demonstrated utility to guide surgical margin assessment for the excision of oral cancer (Farah et al., 2016; Poh et al., 2016; Farah, 2018; Guillaud et al., 2018; Tirelli et al.,

2018b; Schorn et al., 2020). Among vital staining techniques (see Section 4.1.3), toluidine blue and Lugol's iodine have demonstrated utility in the surveillance of patients with a history of oral cancer, when used by experts for tertiary prevention (Epstein et al., 2003; Simões et al., 2017).

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2. REDUCING INCIDENCE OF CANCER OR PRECANCER

2.1 Established risk factors

2.1.1 Tobacco smoking

The carcinogenicity of tobacco smoking was first established by the *IARC Monographs* programme in 1985, including evidence on "the occurrence of malignant tumours of the respiratory tract" (IARC, 1986). Subsequent evaluations have individually listed the oral cavity, oropharynx, and hypopharynx among the multiple affected anatomical sites (IARC, 2004b, 2012b). In most countries, tobacco smoking is the leading cause of oral cancer and oral cancer death (Chang et al., 2015a; Inoue-Choi et al., 2019).

(a) Risk of oral cancer

Observational studies that reported pooled relative risk (RR), meta-RR, or single RR estimates of oral cancer incidence or mortality, whether associated with ever or current cigarette smoking, consistently showed statistically significantly elevated risk estimates (Supplementary Table S2.1, web only; available from https://publications.iarc.fr/617). A meta-analysis of studies published in the 1990s (Gandini et al., 2008), a pooled analysis from the International Head and Neck Cancer Epidemiology (INHANCE) consortium (Wyss et al., 2013), and more recent multi-country (Agudo et al., 2012) and single-country (Maasland et al., 2014) cohort studies in Europe typically reported a 3-fold increase in risk for current smokers or ever-smokers compared with never-smokers (range of RR, 2.11–3.53). Similarly increased risks of oral cancer were reported for smoked tobacco products other than cigarettes (i.e. cigars, pipe, bidi) (Balaram et al., 2002; Wyss et al., 2013).

In non-alcohol users, the INHANCE consortium reported a lower-magnitude pooled risk estimate (odds ratio [OR], 1.35; 95% confidence interval [CI], 0.9–2.01) associated with ever cigarette smoking (Hashibe et al., 2007), whereas a multicentre population-based case–control study in France reported a higher-magnitude risk estimate (OR, 3.2; 95% CI, 1.9–5.3) (Radoï et al., 2015).

The most prevalent tumour histology in the oral cavity is squamous cell carcinoma, and observational studies have reported strong associations with tobacco smoking, whether including all histology subtypes diagnosed (Hashibe et al., 2007; Wyss et al., 2013) or only squamous cell carcinoma (Lee et al., 2009; Maasland et al., 2014).

Reported RRs of oral cancer death in current cigarette smokers (hazard ratio [HR], 5.32; 95% CI, 2.95–9.58) and in daily cigarette smokers (HR, 6.23; 95% CI, 3.42–11.33) were of large magnitude (Inoue-Choi et al., 2019). Significantly increased risks of oral cancer death, with estimates varying between 4.0 and 7.9, were also

reported in primary cigar smokers, including in people who reported no inhalation (Chang et al., 2015a).

RR estimates for oropharyngeal cancer associated with ever or current cigarette smoking have shown larger variations than those for oral cancer, with RR of 3.01 (95% CI, 2.71–3.35) in the INHANCE consortium (Wyss et al., 2013), 5.95 (95% CI, 3.41–10.4) and 8.53 (95% CI, 3.38–21.55) in studies in Europe (Agudo et al., 2012; Maasland et al., 2014), and 1.63 (95% CI, 1.08–2.45) in a study in the USA (Stingone et al., 2013) (Supplementary Table S2.1, web only; available from https://publications.iarc.fr/617).

(i) Smoking intensity, duration, and pack-years

The risk of oral cancer increases with increasing frequency (number of cigarettes smoked per day), duration (in years), and cumulative pack-years of smoking, showing significant dose–response trends (IARC, 2012b; Toporcov et al., 2015) (Supplementary Table S2.2, web only; available from https://publications.iarc.fr/617). Elevated risks of oral cancer associated with current smoking are also evident even at a low daily dose (2 cigarettes) (Polesel et al., 2008). Also, a more pronounced effect for the duration of smoking than for frequency was observed for oral and pharyngeal cancers combined (Di Credico et al., 2019).

The risk of oropharyngeal cancer also increases with increasing frequency, duration, and cumulative pack-years of smoking, showing significant dose–response trends (IARC, 2012b; Toporcov et al., 2015) (Supplementary Table S2.2, web only; available from https://publications.iarc.fr/617).

(ii) Demographic characteristics

Effect estimates from large studies show that the association of smoking with oral cancer is retained when the population is stratified by sex (Agudo et al., 2012) and age at diagnosis (Toporcov et al., 2015) (Supplementary Table S2.1, web only; available from https://publications.iarc.fr/617). A suggested trend of increasing risk of oral cancer with decreasing age at initiation of tobacco smoking appeared to be driven by longer duration of smoking or higher cumulative pack-years of smoking (age at initiation and duration of use are highly correlated), because statistical adjustment for these factors eliminated the originally observed trend (Chang et al., 2019). Geographically, studies in North and South America (Szymańska et al., 2011) and in Europe (Bosetti et al., 2008) have consistently reported positive and significant associations of cigarette smoking with risks of oral cancer and oropharyngeal cancer.

(b) Risk of OPMDs

Tobacco smoking is associated with the occurrence of oral potentially malignant disorders (OPMDs), specifically leukoplakia and erythroplakia, and their malignant transformation, including epithelial dysplasia (Warnakulasuriya et al., 2010; Li et al., 2011; van der Waal, 2014; Mello et al., 2018a). Increased risk of oral submucous fibrosis (OSF) was also reported (Lee et al., 2003) (Supplementary Table S2.1, web only; available from https://publications.iarc.fr/617).

(c) Population attributable fraction

Among studies that reported population attributable fractions (PAFs), there were variations in the anatomical site of the cancer, the definitions of tobacco products, and the geographical span of the populations comprised. Studies reported estimated PAFs of cigarette smoking for oral cancer of 33% (95% CI, 23–48%; Agudo et al., 2012), 21.6% (95% CI, 15.9–25.8%; Anantharaman et al., 2011), and 24.8% (95% CI, 19.6–31.1%; Hashibe et al., 2009), and for oropharyngeal cancer of 49% (95% CI, 36–69%; Agudo et al., 2012) and 29.7% (95% CI, 24.6–33.1%; Anantharaman et al., 2011). Estimates from those studies had at a minimum overlapping

95% CIs; this points to the sizeable proportion of oral and oropharyngeal cancers that are due to tobacco smoking, mainly cigarette smoking. For OPMDs, in particular leukoplakia, the PAF can be even higher (e.g. 56.4% in Taiwan, China; Lee et al., 2003).

(d) Interaction between tobacco smoking and alcohol consumption

Studies assessing the joint effect of tobacco smoking and other established risk factors on the risk of oral cancer are discussed in Section 2.1.7.

2.1.2 Alcohol consumption

(a) Risk of cancer

Consumption of alcoholic beverages has been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme, causing cancers of the oral cavity and pharynx, among multiple other sites (IARC, 2010, 2012b). The risks of oral and oropharyngeal cancer associated with alcohol consumption become more apparent in relation to dose–response and in combination with smoking (Supplementary Table S2.3, web only; available from https://publications.iarc.fr/617). Smoking-adjusted estimates for oral and pharyngeal cancer range from a 4-fold to a 9-fold increased risk; in non-smokers, "the majority of the studies found a strong association with alcoholic beverage consumption among non-smokers with a dose–response relationship" (IARC, 2010). Similar risk estimates were reported across types of alcoholic beverages (Purdue et al., 2009; IARC 2012b; Turati et al., 2013) (Supplementary Table S2.4, web only; available from https://publications.iarc.fr/617).

(i) Drinking intensity and duration

In non-tobacco users, there was a clear dose–risk response with increased frequency of alcohol consumption (drinks per day) for oropharyngeal and hypopharyngeal cancers combined (OR for ≥ 5 drinks per day, 5.50; 95% CI, 2.26–13.4); the dose–risk response was less apparent for oral cancer and for duration of drinking (Hashibe et al., 2007) (Supplementary Table S2.3, web only; available from https://publications.iarc.fr/617).

Three systematic reviews and meta-analyses investigated risks of increasing alcohol intake associated with oral and pharyngeal cancers combined (Tramacere et al., 2010; Turati et al., 2013; Bagnardi et al., 2015). When measured in drinks per day, the pooled RR was 1.21 (95% CI, 1.10–1.33) for ≤ 1 drink per day and increased to 5.24 (95% CI, 4.36–6.30) for heavy alcohol consumption (≥ 4 drinks per day); when measured in grams of ethanol per day, the pooled RR ranged from 1.29 (95% CI, 1.25–1.32) for 10 g ethanol per day to 13.02 (95% CI, 9.87–17.18) for 125 g ethanol per day. Bagnardi et al. (2015) reported pooled risks associated with oral and pharyngeal cancer with increasing alcohol consumption, with RRs of 1.13 (95% CI, 1.00–1.26) for light drinking, 1.83 (95% CI, 1.62–2.07) for moderate drinking, and 5.13 (95% CI, 4.31–6.10) for heavy drinking. Risks were broadly similar in men and in women, for heavy drinking versus non-drinking or occasional drinking.

(ii) Total exposure and frequency of exposure

Lubin et al. (2009) assessed the risk of oral cancer by total exposure and by frequency of use. For equal drink-years (a function of the frequency of alcohol use per day and the duration of drinking in years), higher alcohol intake for a shorter duration conferred a greater risk compared with lower alcohol intake for a longer duration [these data are not shown in the table].

(iii) Gene polymorphisms and ethnic differences

Gene polymorphisms of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), two important enzymes in alcohol metabolism, have been well described; individuals with some of these gene polymorphisms are

at increased risk of oral cancer associated with alcohol consumption (IARC, 2012b). Individuals with homozygous *ADH1B*1/*1* and *ADH1C*1/*1* genotypes are at increased risk of oral cancers (Hashibe et al., 2006; Marichalar-Mendia et al., 2010). *ALDH2*1/*2* heterozygotes are also at increased risk of head and neck cancer (HNC) (Boccia et al., 2009). The *ALDH2*2* variant allele is prevalent in up to 30% of East Asian populations (IARC, 2012b). A significantly increased risk of oral cancer in individuals with *ALDH2*1/*2* genotype was shown in the Japanese population (Nomura et al., 2000).

In their systematic review, Turati et al. (2013) reported minimal differences with respect to geographical area both for drinking overall and for heavy drinking (≥ 4 drinks per day); the RR was lowest for Asia (4.75; 95% CI, 3.14–7.17) and highest for Europe (5.63; 95% CI, 4.09–7.77).

Voltzke et al. (2018) investigated ethnic differences in the relationship between alcohol consumption and risk of oral and oropharyngeal cancer in the USA. They reported consistently stronger risk estimates for Blacks than for Whites (Supplementary Table S2.4, web only; available from https://publications.iarc.fr/617).

(b) Risk of OPMDs

A total of 11 case–control studies investigated the association between alcohol consumption and risk of OPMDs (Supplementary Table S2.5, web only; available from https://publications.iarc.fr/617). Estimates of risk of any OPMDs for alcohol consumption ranged from 0.63 (95% CI, 0.33–1.21) (Li et al., 2011) to 1.4 (95% CI, 0.7–2.7) (Thomas et al., 2003) to 2.7 (95% CI, 1.2–6.3) (Amarasinghe et al., 2010b). Estimates of risk of leukoplakia for alcohol consumption ranged from an OR of 0.22 (95% CI, 0.12–0.37) (Petti and Scully, 2006) to 1.8 (95% CI, 1.1–2.8) (Lee et al., 2003) and to 3.00 (95% CI, 10.27–33.50) for frequent alcohol drinkers (Shiu et al., 2000). In the largest case–control study in India, Hashibe et al. (2000a) reported an OR of 1.4 (95% CI, 1.2–1.7) for ever versus never alcohol consumption. A stronger alcohol–risk association was observed for erythroplakia (OR, 3.0; 95% CI, 1.6–5.7) (Hashibe et al., 2000b). The two case–control studies in Taiwan (China) with data on alcohol consumption and OSF had quite different findings: an OR of 0.68 (95% CI, 0.28–1.64) in men (Yang et al., 2010) and an OR of 1.8 (95% CI, 1.1–3.1) (Lee et al., 2003). No systematic reviews or meta-analyses were identified that assessed the risks of alcohol consumption associated with OPMDs.

(c) Interaction of alcohol consumption with other risk factors

Studies assessing the joint effect of alcohol consumption and other established risk factors on the risk of oral cancer are discussed in Section 2.1.7.

2.1.3 Smokeless tobacco use

In this *Handbook*, the term "smokeless tobacco" refers to products containing tobacco but not including areca nut or other non-tobacco components of betel quid. The composition and use of these products are presented in Section 3.1 and in Table 3.1.

(a) Risk of oral cancer

Use of smokeless tobacco has been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme (IARC, 2007a, 2012b). Meta-analyses have reported RRs for oral and pharyngeal cancers combined ranging from 1.3 to 1.8 (Weitkunat et al., 2007; Boffetta et al., 2008; Lee and Hamling, 2009; IARC, 2012b). Since then, one meta-analysis (Asthana et al., 2019), one pooled analysis (Wyss et al., 2016), and three hospital-based case–control studies that were not included in either the meta-analysis or the pooled analysis (Nasher et al., 2014; Quadri et al., 2015; Gupta et al., 2017) have confirmed the increased risk (Supplementary Table S2.6,

web only; available from https://publications.iarc.fr/617).

Risk estimates by type of smokeless tobacco products vary greatly. Asthana et al. (2019) reported smoking-adjusted ORs ranging from 0.86 (95% CI, 0.58–1.29) for snus/moist snuff to 1.20 (95% CI, 0.80–1.81) for nasal snuff/dipping and 4.18 (95% CI, 2.37–7.38) for oral snuff. Risk estimates for other smokeless tobacco products were also elevated, such as for *naswar* (OR, 11.8; 95% CI, 8.4–16.4; Khan et al., 2019) and for *shammah* (OR, 20.14; 95% CI, 8.23–49.25; Quadri et al., 2015; and 39; 95% CI, 14–105; Nasher et al., 2014).

Smoking-adjusted summary risk estimates are generally higher in women than in men (Weitkunat et al., 2007; Asthana et al., 2019).

Clear and significant positive dose–response relationships were reported between duration of use (in years), frequency of chewing (times per day), smokeless tobacco retention time in the mouth (in minutes), and risk of oral cancer (see Supplementary Table S2.7, web only; available from https://publications.iarc.fr/617).

There was no clear association of smokeless tobacco use with oropharyngeal cancer, with RRs close to 1 in ever-smokers and in never-smokers (Wyss et al., 2016; Supplementary Table S2.6, web only; available from https://publications.iarc.fr/617).

(b) Risk of OPMDs

Numerous studies have consistently shown an increased risk of OPMDs, particularly leukoplakia, in current users or ever-users of snuff or chewing tobacco compared with never-users (Supplementary Table S2.6, web only; available from https://publications.iarc.fr/617). The direction of the risk association was similar by country and type of product chewed (snuff, *naswar*, *shammah*, chewing tobacco, and other products), and a clear dose–response relationship was demonstrated in terms of frequency of chewing (times per day), duration of use (in months), and retention time of the product in the mouth (see Supplementary Table S2.7, web only; available from https://publications.iarc.fr/617). These results were consistent when smoking was accounted for or when restricted to never-smokers.

(c) Population attributable fractions

Based on the GLOBOCAN 2002 incidence data, the proportion of cases attributable to smokeless tobacco use was estimated to be 68.2% in men and 13.6% in women in the Sudan, 52.5% in men and 51.6% in women in India, 50.6% in men and women in other countries in Asia (including Bangladesh, Bhutan, Indonesia, Myanmar, Nepal, Pakistan, and Sri Lanka), 6.6% in men in the USA, and 1.6% in men in Canada (Boffetta et al., 2008). These estimates are similar to those of a more recent report (NCI and CDC, 2014).

2.1.4 Chewing areca nut products (including betel quid) with added tobacco

Areca nut products (including betel quid) with added tobacco include a variety of products with compositions and names that may differ depending on the geographical area where they are used. For more detailed information on the products, see Section 3.1.

(a) Risk of oral cancer

Chewing areca nut products (including betel quid) with added tobacco is an established risk factor for oral cancer and pharyngeal cancer. With the terminology of "betel quid with added tobacco", these products have been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme (IARC, 2004a, 2012b). The RRs for ever-chewers versus never-chewers ranged from 2.1 (95% CI, 2.1–3.4) to 45.9 (95% CI, 25.0–84.1), and the highest RR was reported in women (IARC, 2012b). Since then, one meta-analysis, a large number of case–control studies, and

a few cross-sectional studies, conducted mainly in the Indian subcontinent, have confirmed the clear relationship between areca nut products with added tobacco and increased risk of oral cancer (see Supplementary Table S2.8; web only; available from https://publications.iarc.fr/617).

The risk is higher in women (14.6; 95% CI, 7.6–27.8) than in men (5.4; 95% CI, 3.9–7.4) (Guha et al., 2014). A clear and significant dose–response relationship was reported between the quantity and duration of chewing areca nut with added tobacco and the risk of oral cancer (Madathil et al., 2016; Supplementary Table S2.9, web only; available from https://publications.iarc.fr/617).

(b) Risk of OPMDs

Evidence has accumulated on the association between chewing areca nut products (including betel quid) with added tobacco and the risk of OPMDs (Supplementary Table S2.8, web only; available from https://publications.iarc.fr/617). Risk estimates for chewers versus never-chewers for combinations of OPMDs ranged from 1.4 (95% CI, 0.5–3.7) to 50.5 (95% CI, 21.5–119.5). When OPMDs were considered separately, risk estimates adjusted for tobacco smoking and alcohol consumption ranged from 6.1 (95% CI, 1.8–21.3) to 55.6 (95% CI, 27.4–112.7) for OSF and from 2.5 (95% CI, 1.1–5.6) to 10.0 (95% CI, 8.3–12.0) for leukoplakia. However, when the corresponding estimates were restricted to non-smokers and non-drinkers, the ORs for the different types of OPMDs showed less discrepancy (Jacob et al., 2004).

Significant dose–response relationships were reported between chewing areca nut with added tobacco and the risk of OPMDs, in terms of frequency of chewing (times per day), duration of use (in years), and age at the start of the chewing habit (Supplementary Table S2.9, web only; available from https://publications.iarc.fr/617).

The combined effects of betel quid chewing with other established risk factors are discussed in Section 2.1.7.

(c) Population attributable fractions

In high-prevalence geographical areas, the PAF of chewing betel quid with added tobacco for oral cancer and OPMDs may be very high. In India, the PAF for oral cancer was estimated to be 49.5% for both sexes, and higher in women (63.2%) than in men (44.7%) (Guha et al., 2014). For OPMDs, the PAF was estimated to be 84% in Sri Lanka (Amarasinghe et al., 2010a).

2.1.5 Chewing areca nut products (including betel quid) without tobacco

Areca nut products (including betel quid) without tobacco include a variety of products with specific compositions and names that may differ depending on the geographical area where they are used. For more detailed information on the products, see Section 3.1.

(a) Risk of oral cancer

Chewing areca nut products (including betel quid) without tobacco is an established risk factor for oral cancer. The *IARC Monographs* programme classified separately "betel quid without added tobacco" (IARC, 2004a, 2012b) and areca nut (IARC, 2012b) as carcinogenic to humans (Group 1). Since then, one meta-analysis, a very large number of case–control studies, and a few cohort studies, mainly in Taiwan (China) and some in India, have confirmed the clear relationship between chewing areca nut products without tobacco and increased risk of oral cancer (Supplementary Table S2.10 (web only; available from https://publications.iarc.fr/617).

Guha et al. (2014) reported meta-RRs for oral cancer of 11.0 (95% CI, 4.9–24.8) for Taiwan (China) and 2.4 (95% CI, 1.8–3.2) for the Indian subcontinent. Meta-RRs were also calculated for cancer at specific subsites of the oral cavity for the Indian subcontinent; the highest estimates were reported for the cancer of the palate: 5.1 (95% CI, 1.1–24.9). Guha et al. (2014) also reported a

meta-RR of 2.6 (95% CI, 1.7–3.9) for oropharyngeal cancer.

Significant dose–response relationships were reported between chewing areca nut products without tobacco and the risk of oral cancer (Yang et al., 2014; Hu et al., 2020) or oral cancer death (Wen et al., 2010) in terms of quantity, frequency of use, and duration of use (Supplementary Table S2.11, web only; available from https://publications.iarc.fr/617).

(b) Risk of OPMDs

Evidence has accumulated on the association between chewing areca nut products (including betel quid) without tobacco and the risk of OPMDs (Supplementary Table S2.10, web only; available from https://publications.iarc.fr/617). Risk estimates for chewers versus non-chewers for a combination of OPMDs grouped together ranged from 8.8 (95% CI, 3.2–24.5) to 25.3 (95% CI, 20.8–30.7). When OPMDs were considered separately, risk estimates adjusted for tobacco smoking and alcohol consumption ranged from 4.5 to 65.9 for OSF and from 3.7 to 22.3 for leukoplakia. In a study where estimates were restricted to non-smokers and non-drinkers, the ORs for men and women combined were 22.2 (95% CI, 11.3–43.7) for leukoplakia, 29.0 (95% CI, 5.6–149.5) for erythroplakia, and 56.2 (95% CI, 21.8–144.8) for OSF (Jacob et al., 2004; Supplementary Table S2.10, web only; available from https://publications.iarc.fr/617).

Significant dose–response relationships were reported between chewing areca nut without tobacco and the risk of OPMDs, in terms of frequency of chewing, duration of use, and age at the start of chewing (see Supplementary Table S2.11, web only; available from https://publications.iarc.fr/617).

(c) Population attributable fractions

In high-prevalence geographical areas, the PAF of chewing betel quid without tobacco for oral cancer and OPMDs may be very high. In Taiwan (China), the PAF for oral cancer was estimated to be 57.3% for both sexes (Guha et al., 2014). For OPMDs, the PAFs were estimated to be 85.4% for OSF and 73.2% for leukoplakia, in the southern part of the main island (Lee et al., 2003).

2.1.6 HPV16 infection

(a) Risk of cancer

The *IARC Monographs* programme (IARC, 2012a) determined that there is *sufficient evidence* in humans for the carcinogenicity of human papillomavirus type 16 (HPV16); the virus causes oral cancer and oropharyngeal cancer (IARC, 2012a). The association of HPV16 infection with risk of cancer is heterogeneous in terms of the anatomical site (oral cavity vs oropharynx) as well as the method of assessment of HPV exposure (oral HPV16 DNA, systemic HPV16 L1 antibodies, and systemic HPV16 E6 antibodies). HPV16 infection is associated with a moderately elevated risk of oral cancers; ORs are generally < 5 for oral HPV16 DNA prevalence and HPV16 L1 or E6 seropositivity (Supplementary Table S2.12, web only; available from https://publications.iarc.fr/617).

HPV16 infection is strongly associated with risk of oropharyngeal cancers; the risk estimates from case–control studies range from 14 to > 100 for oral HPV16 DNA prevalence, from 1.1 to > 100 for HPV16 L1 seropositivity, and from 10 to > 200 for HPV16 E6 seropositivity. Reported risk estimates from prospective cohort studies were > 20 for oral HPV16 DNA prevalence, 2–14 for HPV16 L1 seropositivity, and 98–274 for HPV16 E6 seropositivity (Supplementary Table S2.12, web only; available from https://publications.iarc.fr/617). Importantly, HPV16 E6 seropositivity precedes diagnosis of oropharyngeal cancer by several decades, underscoring the temporality of HPV16 exposure and cancer incidence (Kreimer et al., 2013, 2017, 2019).

(b) Risk of OPMDs

A recent systematic review and meta-analysis reported an HPV16 prevalence of 10.8% in OPMDs, primarily leukoplakia, with a similar prevalence in dysplastic and non-dysplastic lesions (de la Cour et al., 2021). [The reporting studies have generally used only HPV16 DNA detection, which does not indicate either an established or active HPV infection, or HPV causality in cancers.]

(c) Population attributable fractions

Globally, the PAF of HPV is ~2% for oral cancers and ~31% for oropharyngeal cancers, and most of the cancers are caused by HPV16 infection (de Martel et al., 2017). There is a wide geographical heterogeneity in HPV etiological fractions for oropharyngeal cancers, ranging from estimates of 40% to > 50% in North America, Europe, Australia and New Zealand, Japan, and the Republic of Korea to estimates of < 15% in most other parts of the world (Ndiaye et al., 2014; de Martel et al., 2017). This heterogeneity may reflect differences in sexual behaviours that are relevant for acquisition of oral HPV infection (e.g. lifetime and recent oral sex behaviours) as well as the relative contributions of HPV infection compared with tobacco use and alcohol consumption across countries and geographical regions (Heck et al., 2010).

2.1.7 Combined effects of established risk factors

Tobacco smoking, alcohol consumption, smokeless tobacco use, chewing areca nut products with or without tobacco, and HPV16 infection are independent risk factors for OPMDs, oral cancers, and oropharyngeal cancers. Combined exposure to more than one of these carcinogens can confer a risk that is at least the sum of the individual risks for each of these carcinogens (risk additivity) or can confer a risk that exceeds the sum (greater-than-additive) or that exceeds the multiplication product (greater-than-multiplicative) of the individual risk estimates. A summary of statistical interactions across these established risk factors is given in Supplementary Table S2.13 (web only; available from https://publications.iarc.fr/617).

(a) Interactions between tobacco smoking and alcohol consumption

Several studies have reported a greater-than-multiplicative interaction between tobacco smoking and alcohol consumption for the risk of oral cancers and pharyngeal cancers (which included cancers of the oropharynx, hypopharynx, and other pharynx) (Blot et al., 1988; Barón et al., 1993; Hayes et al., 1999; Schlecht et al., 1999; Anantharaman et al., 2011). In a meta-analysis of seven observational studies in India and seven studies in Taiwan (China), Petti et al. (2013) found a 6.3-fold increased risk in oral cancer for tobacco smoking and alcohol consumption combined, showing an at least additive effect.

A pooled analysis of 17 case–control studies in Europe and the USA from the INHANCE consortium (Hashibe et al., 2009) reported a greater-than-multiplicative interaction between tobacco use (smoking and chewing) and alcohol consumption for the risk of oral cancer (multiplicative interaction parameter, 3.09; 95% CI, 1.82–5.23) and the risk of pharyngeal cancers (multiplicative interaction parameter, 1.90; 95% CI, 1.41–2.56). The interaction was also greater-than-multiplicative with high exposure to both smoking (> 20 cigarettes per day) and alcohol consumption (> 3 drinks per day); the ORs for joint exposure were 15.49 (95% CI, 7.24–33.14) for oral cancers and 14.29 (95% CI, 7.26–28.15) for pharyngeal cancers. Tobacco use and alcohol consumption collectively accounted for PAFs of 67.1% for oral cancers (23.5% from the tobacco–alcohol interaction effect) and 74.3% for pharyngeal cancers (24.6% from the tobacco–alcohol interaction effect).

(b) Interactions with smokeless tobacco use

Few studies reported formal statistical evaluations of interaction effects of smokeless tobacco use with tobacco smoking or with alcohol consumption on the risk of OPMDs, oral cancers, or oropharyngeal cancers. The few available studies reported the absence of statistical interaction (i.e. consistency with risk additivity) with tobacco smoking or with alcohol consumption on the risk of oral cancers (Winn et al., 1981).

(c) Interactions with chewing betel quid with or without tobacco

Reports of effect modification of the risk conferred by chewing betel quid with or without tobacco by tobacco smoking and/or alcohol consumption have been inconsistent (IARC, 2012b). Some studies have reported the absence of statistical interaction (i.e. consistency with risk additivity) between ever chewing betel quid and ever smoking or ever alcohol consumption for the risk of oral cancers (Subapriya et al., 2007; Muwonge et al., 2008). Some studies have reported a greater-than-additive interaction between ever chewing betel quid and ever smoking in non-drinkers on the risk of oral cancers (Sankaranarayanan et al., 1989). Some studies have reported a greater-than-multiplicative interaction between ever chewing betel quid without tobacco and ever smoking on the risk of oral and pharyngeal cancers (Znaor et al., 2003). A few studies have also reported a greater-than-additive interaction between ever chewing betel quid without tobacco and ever smoking on the risk of OPMDs, particularly leukoplakia (Lee et al., 2003).

Petti et al. (2013) conducted a meta-analysis that included 14 studies – 7 in India (without separation of chewing betel quid with or without tobacco) and 7 in Taiwan, China (chewing betel quid without tobacco) – to evaluate two-way and three-way additive interactions, as measured by relative excess risk due to interaction (RERI) across betel quid chewing, smoking, and alcohol consumption. A statistically significant greater-than-additive interaction was observed between betel quid chewing and tobacco smoking (RERI, 5.48; 95% CI, 1.06–8.20), and a non-significant additive interaction was observed between betel quid chewing and alcohol consumption (RERI, 1.34; 95% CI, –1.29 to 4.50). Importantly, a statistically significant greater-than-additive three-way interaction was observed across betel quid chewing, smoking, and alcohol consumption (RERI, 28.36; 95% CI, 22.92–33.74). Furthermore, the extent of the three-way greater-than-additive interaction was similar in studies in India (RERI, 38.11; 95% CI, 30.05–41.62) and studies in Taiwan, China (RERI, 36.42; 95% CI, 24.87–53.68). Betel quid chewing, tobacco smoking, and alcohol consumption collectively accounted for 74.9% of oral cancers (68.4% from joint effects of all three exposures).

(d) Interactions with HPV16 infection

Reports are sparse for interactions of HPV16 infection with other risk factors for the risk of OPMDs or oral cancers. Most previous evaluations of the interaction of HPV16 infection (as determined by oral HPV16 DNA or systemic HPV16 L1 or HPV16 E6 antibodies) with smokeless tobacco, chewing betel quid with or without tobacco, smoking, and alcohol consumption have included oropharyngeal cancers and have been conducted in Europe and North and South America. Perhaps because of the geographical clustering of these studies, most of the studies have primarily addressed the interaction of HPV16 infection with tobacco smoking and alcohol consumption. Results for the interaction of HPV16 infection with other risk factors have been very inconsistent in the literature: studies have reported a lack of statistical interaction between HPV16 infection and smoking or alcohol consumption on an additive scale (D'Souza et al., 2007; Anantharaman et al.,

2016) or a multiplicative scale (Herrero et al., 2003; Farsi et al., 2017), the presence of a greater-than-additive interaction between HPV16 L1 antibodies and smoking (Schwartz et al., 1998), greater-than-additive interactions between oral HPV16 DNA and alcohol consumption (Smith et al., 2004), and less-than-multiplicative interactions between HPV16 E6 antibodies and smoking (Ribeiro et al., 2011) and between HPV16 L1 antibodies and smoking and HPV16 L1 antibodies and alcohol consumption (Applebaum et al., 2007). [Despite this inconsistency, smoking and heavy alcohol consumption are associated with increased risk of both HPV16-positive and HPV16-negative oropharyngeal cancers and, at the very least, should be considered to be independent risk factors for oropharyngeal cancers.]

2.2 Additional potential risk factors for oral cancer

A proportion of oral cancers cannot be attributed to the major established risk factors (Sections 2.1.1–2.1.6), particularly oral cancers that occur in women and young people. There is a substantial amount of literature on several other putative risk factors, for some of which there is only little evidence.

2.2.1 Environmental factors

(a) Second-hand smoke

The most recent evaluation by the *IARC Monographs* programme (IARC, 2012b) confirmed that second-hand tobacco smoke (also called environmental tobacco smoke, passive smoking, or involuntary smoking) is carcinogenic to humans (Group 1), although evidence for oral cancer was sparse. A recent meta-analysis of five case–control studies reported a positive association between exposure to second-hand smoke and risk of oral cancer (overall OR, 1.51; 95% CI, 1.20–1.91). A duration of exposure of > 10 or 15 years conferred a higher risk of oral cancer (OR, 2.07; 95% CI, 1.54–2.79) compared with non-exposed people (Mariano et al., 2022).

(b) Indoor air pollution

The *IARC Monographs* programme classified indoor emissions from household combustion of coal as carcinogenic to humans (Group 1), with *sufficient evidence* for lung cancer (IARC, 2012b). More recently, a meta-analysis of 4 studies found a significant risk from household air pollution for the development of oral cancer (OR, 2.44; 95% CI, 1.87–3.19) (Josyula et al., 2015). Notably, a high incidence of oral cancer was reported in chefs engaged in regular cooking (Foppa and Minder, 1992). Indoor air pollution could be a risk factor that increases risk in women more than in men.

(c) Heavy metals in soil

Most of the studies on heavy metals in soil and risk of oral cancer are from Taiwan (China), particularly from Changhua County, which has a higher environmental heavy metal concentration than the other counties. Studies pointed to arsenic and nickel in farm soils as new risk factors for oral cancer (Su et al., 2010). Significant associations between oral cancer and blood levels of nickel and/or chromium have been reported after controlling for potential confounders (Chiang et al., 2011; Yuan et al., 2011). Also, Tsai et al. (2017) reported that 68.8% of leukoplakia with subsequent malignant transformation occurred in people exposed to high levels of nickel in soil.

(d) Occupational exposures

Increased risks due to occupational exposure to heavy metals were reported, for oral cancer due to exposure to metal dust containing chromium and nickel (OR, 3.4; 95% CI, 1.7–7.0) (Tisch et al., 1996) and for risk of tongue cancer due to exposure to chromium(VI) compounds (Tisch

and Maier, 1996). A recent systematic review analysed risk of HNC and occupational exposure to formaldehyde, wood dust, metal, coal particles, and asbestos, but it included only few studies on oral cancer (Awan et al., 2018).

2.2.2 Lifestyle factors

(a) Maté drinking

Maté is a beverage prepared from the leaves of the *Ilex paraguariensis* plant and is usually drunk very hot with a metal straw in Argentina, southern Brazil, Chile, Paraguay, and Uruguay. The *IARC Monographs* programme concluded that drinking very hot beverages – at temperatures above 65 °C – is probably carcinogenic to humans (Group 2A) (IARC, 2018). Two meta-analyses reported a significant association between maté drinking and oral cancer (OR, 2.11; 95% CI, 1.39–3.19) (Dasanayake et al., 2010) and oral and oesophageal cancers (OR, 1.49; 95% CI, 1.08–2.05) (Mello et al., 2018b). The 2018 World Cancer Research Fund (WCRF) reported that the evidence suggesting that greater consumption of maté increases the risk of oral cancer is limited (WCRF, 2018).

(b) Khat chewing

Khat (*Catha edulis* Forsk), also known as qat, is consumed in Yemen and in East Africa, particularly in Somalia and Ethiopia, as well as in the global diaspora from this region. Although khat chewing has detrimental effects on teeth and the periodontium, a systematic review (El-Zaemey et al., 2015) and a narrative review (Al-Maweri et al., 2018) did not demonstrate any significant association between khat use and oral cancer.

(c) Cannabis smoking

Evidence is lacking on the association between smoking of cannabis (also called marijuana) and oral cancer. Cannabis smoking is often combined with heavy tobacco use and alcohol consumption, which makes it difficult to properly adjust for confounding and interactions. One case–control study, in the USA, reported an increased risk of HNC in regular marijuana users (Zhang et al., 1999), whereas an analysis from the INHANCE consortium (Marks et al., 2014) found no such risk.

(d) Opium consumption

The *IARC Monographs* programme recently evaluated the carcinogenicity of opium consumption, smoked or ingested (IARC, 2021). One ecological study, one case–control study, and one large case series (Fahmy et al., 1983; Razmpa et al., 2014; Rashidian et al., 2016) reported that opium use was associated with increased risk of oral cancer; however, these studies had some limitations, and the evidence was considered to be inadequate (Warnakulasuriya et al., 2020).

(e) Mouthwash use

Several case–control studies have examined the risk of mouthwash use for the causation of oral cancer. Several reviews and meta-analyses were performed, which reported conflicting evidence (Lewis and Murray, 2006; McCullough and Farah, 2008; La Vecchia, 2009; Gandini et al., 2012; Currie and Farah, 2014). A risk quantitative meta-analysis (Gandini et al., 2012) and an independent expert group assembled by the United States Food and Drug Administration (FDA, 2003) found no excess risk of oral cancer from use of mouthwash containing or not containing alcohol. However, daily use of mouthwash over a prolonged period (> 35 years) was suggested to cause oral cancer by an international consortium (Boffetta et al., 2016). [It is likely that people with oral cancer may use mouthwashes to mask their halitosis or to control symptoms of the disease. In many of the case–control studies, reverse causation was not considered.]

2.2.3 Demographic factors

Studies conducted in the United Kingdom and in several countries in Europe indicate that most patients with oral cancer have lower socioeconomic status, live in low-resource settings, or have jobs with low occupational social prestige (Woolley et al., 2006; Conway et al., 2008, 2021). Also, patients with oral cancer living in deprived areas had an increased risk of death from oral cancer (RR, 1.28; 95% CI, 1.11–1.47) compared with people living in affluent areas (Edwards and Jones, 1999).

In contrast, a study in Brazil reported no significant risk of oral cancer in people with lower education levels (OR, 1.71; 95% CI, 0.74–3.96) (Andrade et al., 2015). A study in Scotland was also inconclusive regarding the individual components of socioeconomic status and the risk of HNC (Conway et al., 2010).

2.2.4 Orodental factors

(a) Chronic mechanical irritation

Chronic mechanical irritation to the oral mucosa may, over a period of time, lead to OPMDs and oral cancer (Piemonte et al., 2010, 2018). Because of loss of the protective barrier of the mucosa, chronic mechanical irritation arising from dental factors could facilitate the entry of carcinogens or infections into deeper layers of the squamous epithelium (Gilligan et al., 2017).

Poor dentition (faulty restorations, malpositioned teeth, or sharp or broken teeth due to decay or fractures) and ill-fitting prosthesis have been associated with risk of oral cancer in several case–control studies (Lockhart et al., 1998; Velly et al., 1998; Rosenquist, 2005; Vaccarezza et al., 2010; Bektas-Kayhan et al., 2014; Huang et al., 2015; Li et al., 2015; Chen et al., 2018; Piemonte and Lazos, 2018) (Supplementary Table S2.14, web only; available from https://publications.iarc.fr/617). A meta-analysis based on 9 studies (mostly in the USA) also found that ill-fitting dentures substantially increased the risk of oral cancer (OR, 3.90; 95% CI, 2.48–6.13) (Manoharan et al., 2014).

(b) Oral hygiene

Several studies have provided evidence that advanced periodontal disease due to poor oral hygiene may be an independent risk factor for oral cancer and HNC (Guha et al., 2007; Meyer et al., 2008). Bleeding gums (OR, 3.94; 95% CI, 2.49–6.25) and dental check-ups only at the time of pain (OR, 3.84; 95% CI, 2.38–6.20) were both associated with significantly increased risk after adjustment for potential confounders (Gupta et al., 2017). The INHANCE consortium reported a strong association of poor oral health with oral cancer (OR for worst oral health vs best oral health, 3.12; 95% CI, 2.08–4.68) (Hashim et al., 2016). Three meta-analyses reported that periodontal disease (OR, 3.08; 95% CI, 1.60–3.93) (Zeng et al., 2013a), tooth loss (OR, 1.72; 95% CI, 1.26–2.36) (Zeng et al., 2013b), and infrequent tooth brushing (OR, 1.73; 95% CI, 1.36–2.20) (Zeng et al., 2015) were associated with increased risk of oral cancer or head and neck squamous cell carcinoma.

(c) Oral infections

Several reviews have examined the published evidence on the relationship between the oral microbiome and oral squamous cell carcinoma (OSCC) (Whitmore and Lamont, 2014; Gholizadeh et al., 2016; Perera et al., 2016; Chen et al., 2017). In multiple studies, significantly higher levels of *Porphyromonas* spp. and *Fusobacterium* spp. were found in OSCC tissues than in healthy mucosa (Nagy et al., 1998; Katz et al., 2011; Pushalkar et al., 2012). The presence of specific species of bacteria in tumour tissue (Zhang et al., 2020) adds strength to the specificity of these studies.

High lipopolysaccharide levels in cancerous conditions were indicative of Gram-negative

bacteria found in the subgingival microflora, which have lipopolysaccharide in their cell wall, thus causing lipopolysaccharide-induced inflammation (Kavarthapu and Gurumoorthy, 2021). A systematic review of 14 in vitro studies and 3 studies in animal models proposed a role of *Porphyromonas gingivalis* in the development of OSCC through epithelial–mesenchymal transition of malignant cells, neoplastic proliferation, and tumour invasion (Lafuente Ibáñez de Mendoza et al., 2020).

A nested case–control study conducted in prospective studies in two populations in the USA found that abundance of *Corynebacterium* and *Kingella* was associated with a decreased risk of head and neck squamous cell carcinoma, whereas *Parvimonas micra* and *Neisseria sicca* were associated with a decreased risk of oral cancer. However, an unnamed *Actinomyces* was associated with an increased risk of oral cancer (Hayes et al., 2018).

Several studies and meta-analyses have investigated the presence of Epstein–Barr virus in oral carcinoma, with a reported prevalence ranging from 0% to 100% (Acharya et al., 2015; She et al., 2017; de Lima et al., 2019). A meta-analysis of 8 case–control studies reported a significant positive association between Epstein–Barr virus infection and oral lichen planus (OLP) (Ashraf et al., 2020).

Candida is frequently present in oral biopsy samples of moderate and severe dysplasia, and significant dysplastic changes have been noted in the epithelium of candidal leukoplakia harbouring *Candida* species (McCullough et al., 2002; Shukla et al., 2019). A recent systematic review on candidal leukoplakia (Shukla et al., 2019) identified three studies, which reported malignant transformation ratios of 2.5%, 6.5%, and 28.7%.

2.2.5 Systemic factors

(a) Immunosuppression

Immunosuppression has also been shown to be a mechanism that can lead to cancer (Baan et al., 2019). A few case series of secondary oral cancer after allogeneic haematopoietic cell transplantation or after renal transplantation have been published (King et al., 1995; van Leeuwen et al., 2009; Santarone et al., 2021). The studies of Laprise et al. (2019) and van Leeuwen et al. (2009) confirmed that immunosuppressive agents (azathioprine and cyclosporine) used after organ transplantation may increase susceptibility to lip and oral cancer.

Patients with inflammatory bowel disorders (e.g. Crohn disease) who may take long-term immunosuppressive agents (e.g. azathioprine) may be at increased risk of tongue or oral cancer (Li et al., 2003; Katsanos et al., 2016).

In a study conducted during the pandemic of HIV infection before the era of combined antiretroviral therapy (cART), patients diagnosed with HIV disease did not have an increased risk of oral cancer (Hille and Johnson, 2017). However, the rate of HPV-associated HNC is higher in people living with HIV (Beachler and D'Souza, 2013).

(b) Obesity, underweight, and body mass index

Obesity is an established risk factor for many cancer types (Arnold et al., 2016). The 2018 WCRF report, which analysed 25 studies, reported that obesity marked by BMI, waist circumference, and waist-to-hip ratio probably increased the risk of oral and pharyngeal cancers (WCRF, 2018). In contrast, in a pooled data analysis from 15 case–control studies, ORs were increased in underweight (BMI < 18.5 kg/m^2) compared with normal weight (BMI, 18.5–24.9 kg/m^2) and decreased in overweight and obese categories (BMI ≥ 25 kg/m^2) for oral cancer and other HNC; ORs were similar in men and women (Lubin et al., 2011). A more

recent study from the INHANCE consortium also found that low BMI (i.e. < 18.5 kg/m^2) was associated with higher risk of HNC (Gaudet et al., 2015).

A study in Sri Lanka found that low BMI (< 18.5 kg/m^2) was a significant independent risk factor for the development of OPMDs (Amarasinghe et al., 2013).

(c) Metabolic syndrome

In two studies of people with metabolic syndrome (Chang et al., 2015b; Siewchaisakul et al., 2020) the condition was found to be significantly associated with OPMDs. Three components of metabolic syndrome were reported to be significantly associated with OPMDs: central obesity, hypertriglyceridaemia, and hyperglycaemia (Siewchaisakul et al., 2020).

(d) Haematinic and micronutrient deficiency

Haematinic deficiency (e.g. deficiency of iron, folate, or vitamin B12) can cause histopathological changes in the oral mucosa and/or clinically detectable OPMDs, presumably by interfering in epithelial proliferation and/or maturation (Ranasinghe et al., 1983). A recent study reported significantly higher frequencies of haematinic deficiencies and hyperhomocysteinaemia in patients with OPMDs than in healthy controls (Wu et al., 2019).

2.2.6 Familial or genetic predisposition

Sporadic case reports proposed that oral cancer could be familial (Ankathil et al., 1996). A case–control study in Italy and Switzerland reported that a family history of oral cancer, pharyngeal cancer, or laryngeal cancer is a strong determinant of risk of oral and pharyngeal cancer, independent of tobacco use and alcohol consumption (Garavello et al., 2008). The INHANCE consortium reported that a family history of cancer in first-degree relatives increased the risk of oral cancer (OR, 1.53; 95% CI, 1.11–2.11) (Negri et al., 2009).

Of the many familial cancer syndromes, patients with Fanconi anaemia, xeroderma pigmentosum, Li–Fraumeni syndrome, Bloom syndrome, ataxia–telangiectasia, and Cowden syndrome have shown an increased susceptibility to oral cancer due to genetic instability, and those with Fanconi anaemia have the strongest predisposition (Furquim et al., 2018; Amenábar et al., 2019). Dyskeratosis congenita (also called Zinsser–Cole–Engman syndrome) is a rare hereditary condition with predisposition to leukoplakia of the tongue that could transform into cancer in early life (Handley and Ogden, 2006).

A genome-wide association study of oral and pharyngeal cancers with 6034 cases and 6585 controls in Europe, North America, and South America detected 8 loci (regions) contributing to susceptibility to oral and pharyngeal cancers. Oral cancer was associated with two new regions (2p23.3 and 9q34.12) and with known cancer loci (9p21 and 5p15.33). Oral and pharyngeal cancers combined were associated with loci at 6p21.32, 10q26.13, and 11p15.4 (Lesseur et al., 2016).

The TP53 codon 72 polymorphism has been suggested to play a role in cancer susceptibility, and more specifically susceptibility to HPV-associated cancers. An association between p53 gene variants and oral cancer susceptibility was reported in India (Patel et al., 2013). A study in Argentina reported that the frequency of TP53 codon 72 Pro72variant was higher in patients with OSCC and OPMDs than in controls (Zarate et al., 2017), and a study in China (Hou et al., 2015) reported that p53 Arg72Pro polymorphism together with HPV infection may jointly alter an individual's susceptibility to oral cancer. A meta-analysis of 11 studies suggested that in the absence of HPV infection the TP53 codon 72 polymorphism (Arg vs Pro) is not associated with the risk of OSCC (Zeng et al., 2014).

2.3 Impact upon quitting

For the evaluation of studies in humans on the potential reduction in cancer risk due to reduction or cessation of exposure to a risk factor for oral cancer, intervention studies, cohort studies, case–control studies, and cross-sectional studies were eligible for inclusion. The selection was limited to studies of established risk factors, i.e. tobacco smoking, consumption of alcoholic beverages, use of smokeless tobacco, and chewing of areca nut (including betel quid) with added tobacco or without tobacco [hereafter described as the exposure]. Only studies that evaluated separately the effect on cancer of the oral cavity, or of the oral cavity and the pharynx combined (oropharynx and/or hypopharynx) were included. Studies of cancer incidence and cancer mortality were eligible for inclusion. In addition, studies on OPMDs, such as oral leucoplakia or erythroplakia, were included as supporting evidence.

Only those studies that compared former exposure and current exposure with never exposure, and former exposure with current exposure, were included. Studies that compared former exposure versus never exposure but not current exposure versus never exposure were excluded. No studies reported on reduction of exposure and risk of cancer or OPMDs.

For the evaluation of cessation of chewing areca nut with added tobacco and chewing areca nut without tobacco, in addition to the analyses in published studies, Working Group performed primary analyses of unpublished data on the associations with risk of oral cancer or risk of OPMDs. Table 2.15 shows the number of analyses for each exposure, by study design; some studies contributed evidence to more than one group.

2.3.1 Tobacco smoking

(a) Risk of oral cancer and oropharyngeal cancer

Volume 11 of the *IARC Handbooks of Cancer Prevention* evaluated the scientific evidence available until the first trimester of 2006 on the effects of smoking cessation on the risk of cancer (IARC, 2007b). The Working Group concluded that for oral and pharyngeal cancer, the risk "is lower in former smokers than in otherwise similar current smokers", the relative reduction in risk increases with duration of quitting, and the RR after ≥ 2 decades of smoking cessation returns to that in never-smokers (IARC, 2007b).

(i) Overview of studies

The Working Group assessed all the available studies published since 2006. Studies that reported risk estimates in former smokers by time since quitting smoking were considered to be more informative and included individual cohort studies (Freedman et al., 2007; Maasland et al., 2014), a pooled analysis of 17 case–control studies (Marron et al., 2010), a pooled analysis of 2 case–control studies (Bosetti et al., 2008), and 4 individual case–control studies (De Stefani et al., 2007; Lee et al., 2009; Varela-Lema et al., 2010; Radoï et al., 2013a). Two mortality cohort studies that included former smokers but did not report risk estimates by duration of smoking cessation were identified (Ide et al., 2008; Christensen et al., 2018). Most of the studies included male and female participants; two studies included only male participants (De Stefani et al., 2007; Varela-Lema et al., 2010).

The studies varied with respect to the definitions of study population, cancer outcome, and former smoker, the categorization of time since quitting smoking, the reference group used to estimate RRs, and the extent of adjustment for potential confounders. The definition of former smoker, when available, varied from having quit smoking ≥ 6 months before enrolment to having

Table 2.15 Number of studies that assess quitting exposure to the risk factor and reduction in risk of oral cancer or OPMDs

Risk factor	Type of studies	Number of studies	
		Oral cavity or oral cavity and pharynx	OPMDs
Tobacco smoking	Cohort	4	1
	Case–control	4	6
	Cross-sectional	0	1
	Pooled analysis (of case–control studies)	2	0
	Meta-analysis	0	0
Alcoholic beverage consumption	Cohort	3	0
	Case–control	6	7
	Pooled analysis (of case–control studies)	1	0
	Meta-analysis	0	0
Smokeless tobacco use	Cohort	2	4
	Case–control	4	2
	Cross-sectional	0	2
	Pooled analysis	0	0
	Meta-analysis by the Working Group (of cohort studies and case–control studies)	1	1
Chewing areca nut products (including betel quid) with added tobacco	Cohort (published/primary analysis[a])	2/1	1
	Case–control (published/primary analysis[a])	3/1	2
	Pooled analysis	0	0
	Meta-analysis (of cohort studies and case–control studies)	1	0
Chewing areca nut products (including betel quid) without tobacco	Cohort (published/primary analysis[a])	0/3	0/3
	Case–control (published/primary analysis[a])	4/1	3/1
	Cross-sectional	0	2
	Meta-analysis (of case–control studies)	1	0

OPMDs, oral potentially malignant disorders.
[a] Primary analyses of unpublished data performed by the Working Group.

quit > 2 years before enrolment. The duration of smoking cessation was reported in at least two categories, usually using a cut-off point of 10 years; few studies used more categories of duration of smoking cessation. Few studies controlled for cumulative smoking or presented estimates by time since quitting smoking stratifying by quantity smoked or cumulative smoking. Only the pooled analysis and three case–control studies used current smokers as the reference group to assess reductions in RR associated with quitting smoking. Outcomes of oral cancer, oropharyngeal and hypopharyngeal cancer, pharyngeal cancer, and oral and pharyngeal cancer were used to report RRs associated with smoking cessation. No studies reported risk of oropharyngeal cancer alone or risk of oropharyngeal cancer death. In most studies, the smoked tobacco product was cigarettes.

(ii) Cohort studies

See Table 2.16.

Freedman et al. (2007) reported on the association of smoking status and HNC in men and in women in the prospective United States National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, which enrolled 476 211 participants from October 1995 until the end of 2000. Former smokers were defined as people who had quit smoking > 1 year before the date of completing

Table 2.16 Cessation of tobacco smoking and risk of oral cancer and/or pharyngeal cancer – cohort studies

Reference Location	Study population, number of participants, follow-up period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/number in cohort	RR or HR (95% CI)	Adjustments/comments
Cancer incidence						
Freedman et al. (2007) USA	Prospective NIH-AARP Diet and Health Study, following up 283 691 men and 192 520 women; aged 50–71 yr, in 6 states of the USA, from 1995 until the end of 2000; 759 head and neck cancers, 310 oral cancers, and 139 oropharyngeal/ hypopharyngeal cancers were diagnosed	SCC of the oral cavity (lips, tongue, gums, palate, floor of the mouth, and other parts of the mouth) and oro-hypopharynx (oropharynx, tonsils, hypopharynx, pyriform sinus, and pharynx not otherwise specified)	Cigarette smoking:	Oral cancer:	HR:	Current smokers included regular smokers and people who stopped smoking within the year before enrolment Estimates adjusted for age at entry into cohort, BMI, education level, alcohol consumption, vigorous physical activity, usual activity throughout the day, fruit intake, vegetable intake, and total energy
				Men:		
			Never-smokers	54	1.0 (ref)	
			Current smokers	71	2.99 (2.05–4.38)	
			Former smokers	104	1.00 (0.72–1.40)	
			Duration of cessation (yr):			
			1–4	18	2.49 (1.45–4.28)	
			5–9	17	1.29 (0.74–2.25)	
			≥ 10	69	0.83 (0.58–1.19)	
					$P_{trend} < 0.001$	
				Women:		
			Never-smokers	14	1.0 (ref)	
			Current smokers	42	7.57 (4.02–14.28)	
			Former smokers	25	2.10 (1.08–4.06)	
			Duration of cessation (yr):			
			1–4	8	6.18 (2.57–14.86)	
			5–9	4	1.88 (0.62–5.75)	
			≥ 10	13	1.53 (0.72–3.27)	
					$P_{trend} < 0.001$	
			Cigarette smoking:	Oro/hypopharyngeal cancer:		
				Men:		
			Never-smokers	16	1.0 (ref)	
			Current smokers	41	5.29 (2.88–9.73)	
			Former smokers	49	1.52 (0.86–2.70)	

Table 2.16 (continued)

Reference Location	Study population, number of participants, follow-up period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/number in cohort	RR or HR (95% CI)	Adjustments/comments
Freedman et al. (2007) (cont.)			Duration of cessation (yr):			
			1–4	8	3.42 (1.45–8.07)	
			5–9	13	3.05 (1.45–6.40)	
			≥ 10	28	1.10 (0.59–2.05)	
					P_{trend} < 0.001	
				Women:		
			Never-smokers	3	1.0 (ref)	
			Current smokers	16	11.39 (3.21–40.40)	
			Former smokers	14	5.29 (1.50–18.61)	
			Duration of cessation (yr):			
			1–4	4	12.57 (2.78–56.86)	
			5–9	3	6.11 (1.22–30.60)	
			≥ 10	7	3.81 (0.98–14.89)	
					P_{trend} < 0.001	
Maasland et al. (2014) The Netherlands	The Netherlands Cohort Study, initiated in 1986, enrolled 120 852 men and women aged 55–69 yr from 204 municipal population registers in the Netherlands. In 17.3 yr of follow-up, 110 oral cancers and 83 oropharyngeal/ hypopharyngeal cancers were diagnosed	Microscopically confirmed SCC of the head and neck, including the oral cavity and the oropharynx and hypopharynx	Smoking:	Oral cancer:		Former smoker status not defined, but from categorization of the variable "years since quitting" recorded at baseline, it is evident that people who quit within the year of enrolment or earlier were considered former smokers. Estimates adjusted for age (years), sex, and alcohol consumption (grams of ethanol per day; continuous). Analysis by duration of cessation also adjusted by pack-years of cigarette smoking (continuous)
			Never-smokers	29	1.0 (ref)	
			Current smokers	57	2.03 (1.16–3.56)	
			Former smokers	24	–	
			Duration of cessation (yr):			
			> 0 – < 10	11	0.84 (0.39–1.83)	
			10 – < 20	8	0.78 (0.32–1.86)	
			≥ 20	5	0.63 (0.22–1.81)	
					P_{trend} < 0.004	
			Smoking:	Oro/hypopha-ryngeal cancer:		
			Never-smokers	6	1.0 (ref)	
			Current smokers	55	8.10 (3.14–20.87)	
			Former smokers	22	–	

Table 2.16 (continued)

Reference Location	Study population, number of participants, follow-up period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/number in cohort	RR or HR (95% CI)	Adjustments/comments
Maasland et al. (2014) (cont.)			Duration of cessation (yr)			
			> 0 – < 10	8	2.48 (0.77–7.93)	
			10 – < 20	8	3.29 (1.04–10.39)	
			≥ 20	6	3.35 (0.97–11.55)	
					P_{trend} < 0.001	
Cancer mortality						
Ide et al. (2008) Japan	The Japan Collaborative Cohort Study for Evaluation of Cancer Risk covered 45 geographical areas in the country, enrolling 46 465 men and 64 327 women aged 40–79 yr in 1988–1990, with 12.5 yr of follow-up and identification of 52 oral and pharyngeal cancer deaths (41 in men)	Annual ascertainment of oral and pharyngeal cancer deaths, identified by ICD-10 codes C01–C14, excluding C07–C08 (salivary gland cancer) and C11 (nasopharyngeal cancer)	Smoking status:	Oral and pharyngeal cancer deaths:		Current or former smokers not defined RR of death adjusted for age, alcohol consumption, consumption of green tea, preference for salty foods, and consumption of green and yellow vegetables
				Men:		
			Non-smokers	5	1.0 (ref)	
			Current smokers	29	2.6 (1.0–6.7)	
			Former smokers	7	0.9 (0.3–3.0)	
Christensen et al. (2018) USA	The National Longitudinal Mortality Study included a representative sample of civilian, non-institutionalized men and women aged 35–80 yr (n = 357 420) who completed the Tobacco Use Supplement of the national Current Population Survey starting in 1985, with death ascertainment until the end of 2011	Lip, oral, and pharyngeal cancer deaths (ICD-10 codes C00–C14)	Exclusive cigarette smoking:	Oral and pharyngeal cancer deaths:		Former smokers were defined as people who had ever smoked ≥ 100 cigarettes but were non-smokers at the time of the baseline survey Risk of death (HR) adjusted for age, sex, race/ethnicity, education level, and year of survey Estimates not adjusted for alcohol consumption, and therefore probably confounded
			Never-smokers	31	1.0 (ref)	
			Current smokers	79	9.02 (5.78–14.09)	
			Former smokers	50	2.70 (1.66–4.39)	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; NIH-AARP, United States National Institutes of Health-American Association of Retired Persons; ref, reference; RR, relative risk; SCC, squamous cell carcinoma; yr, year or years.

the baseline questionnaire, which also recorded time since quitting smoking.

The RRs of oral cancer in former smokers decreased progressively with increasing time since quitting smoking in men (from HR for 1–4 years since quitting, 2.49; 95% CI, 1.45–4.28 to HR for > 10 years since quitting, 0.83; 95% CI, 0.58–1.19) and in women (from HR for 1–4 years since quitting, 6.18; 95% CI, 2.57–14.86 to HR for > 10 years since quitting, 1.53; 95% CI, 0.72–3.27); these estimates were lower than the RRs in current male smokers (HR, 2.99; 95% CI, 2.05–4.38) and current female smokers (HR, 7.57; 95% CI, 4.02–14.28). RRs of oral cancer were steadily higher in women than in men, whether in former smokers or in current smokers compared with never-smokers. [A larger proportion of oral cancers in men (23%) than in women (17%) were diagnosed in never-smokers, which may suggest that there are factors increasing the background risk in men more than in women, and this differential appears to lower the magnitude of the RRs compared with never-smokers reported in men with respect to the RRs reported in women.]

The elevated RRs of oropharyngeal and hypopharyngeal cancer in former smokers compared with never-smokers decreased with increasing time since quitting smoking in men (from HR for 1–4 years since quitting, 3.42; 95% CI, 1.45–8.07 to HR for > 10 years since quitting, 1.10; 95% CI, 0.59–2.05) and in women (from HR for 1–4 years since quitting, 12.6; 95% CI, 2.78–56.86 to HR for > 10 years since quitting, 3.81; 95% CI, 0.98–14.89); although these estimates remained elevated, they were of lower magnitude than the RRs in current male smokers (HR, 5.29; 95% CI, 2.88–9.73) and current female smokers (HR, 11.39; 95% CI, 3.21–40.40).

[The Working Group noted that this is one of the very few studies that investigated the association with quitting smoking separately in men and in women, and cautioned about interpreting differences in RR by sex.]

Maasland et al. (2014) reported on the Netherlands Cohort Study, which was initiated in 1986 and enrolled 120 852 men and women aged 55–69 years from 204 Dutch municipal population registers. Follow-up for cancer incidence, extended until 2003, was done through annual record linkage to the Netherlands Cancer Registry and the nationwide network of pathology registries. Former smoker status was not defined. The RR estimates for oral cancer in former smokers by time since quitting smoking were < 1, and the CIs included 1. A tendency of decreasing RR with increasing duration of quitting was observed, from RR for > 0 to < 10 years since quitting, 0.84 (95% CI, 0.39–1.83) to RR for ≥ 20 years since quitting, 0.63 (95% CI, 0.22–1.81); for current smokers, RR was 2.03 (95% CI, 1.16–3.56; P_{trend} < 0.004). A similar tendency of decreasing RR with increasing duration of quitting was observed for oropharyngeal and hypopharyngeal cancer; the magnitude of the RR at any duration of quitting was still elevated in former smokers with respect to never-smokers but was substantially lower than the RR in current smokers.

Two cohort studies reported risk of death in former smokers and current smokers using non-smokers as the reference group (Ide et al., 2008; Christensen et al., 2018). The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, conducted in 45 geographical areas in the country, enrolled 46 465 men and 64 327 women who were followed up for an average of 12.5 years (Ide et al., 2008). In men, the RR of oral and pharyngeal cancer death in former smokers compared with non-smokers was 0.9 (95% CI, 0.3–3.0), and the risk of death in current smokers was more than twice that in non-smokers (RR, 2.6; 95% CI, 1.0–6.7). In women, the risk of oral and pharyngeal cancer death in current smokers compared with non-smokers was substantially higher (RR, 8.2; 95% CI, 2.1–32.1). [The Working Group noted the lack of a definition of former smoker and the absence of deaths in female

former smokers, which precluded the generation of a mortality risk estimate. No estimates by time since quitting were available.]

The National Longitudinal Mortality Study includes a representative sample of the civilian, non-institutionalized population of the USA, including men and women. For the analysis reported by Christensen et al. (2018), cohort members who completed the tobacco use questionnaire included 357 420 participants (excluding exclusive smokeless tobacco users and users of multiple types of tobacco). Former smokers were defined as people who had ever smoked ≥ 100 cigarettes but were non-smokers at the time of the survey. The definition of former smoker did not specify the duration of cessation.

The RR of death from oral and pharyngeal cancer in former smokers was almost 3 times that in never-smokers (RR, 2.70; 95% CI, 1.66–4.39) and was much lower than the RR of death in current smokers (RR, 9.02; 95% CI, 5.78–14.09). [The Working Group noted that, given that study participants were classified as former smokers or current smokers at baseline and cancer mortality was ascertained years later, changes in smoking status during follow-up could have introduced misclassification of exposure in the cohort, which could lead to underestimation or overestimation of the reported risks. Risk estimates may be confounded by lack of adjustment for alcohol consumption.]

(iii) Case–control studies

See Table 2.17.

Marron et al. (2010) reported on a large individual-level data pooled analysis of 17 case–control studies exploring the association of smoking cessation and HNC within the INHANCE consortium, reporting ORs for oral cancer and oro-hypopharyngeal cancer by time since quitting smoking using current smokers as the reference group. The risk of oral cancer decreased with quitting smoking compared with continuing smoking, and the reduction in risk became more pronounced the longer the cessation interval (P_{trend} < 0.01). In recent quitters (from 13 months to 4 years since quitting), the OR was 0.65 (95% CI, 0.52–0.80). With ≥ 20 years since quitting, the RR decreased to 0.19 (95% CI, 0.15–0.24), a RR similar in magnitude and precision to the RR reported for never-smokers (OR, 0.19; 95% CI, 0.14–0.27). Similarly, for oropharyngeal and hypopharyngeal cancers combined, the magnitude of the reduction in risk increased progressively with longer time since quitting (P_{trend} < 0.01). The reduction in risk was already evident in recent quitters (OR for > 1–4 years since quitting, 0.72; 95% CI, 0.52–1.00) and became more pronounced the longer the cessation interval, until the RR reached that in never-smokers after ≥ 20 years of cessation. [The Working Group recognized the large sample size of this pooled study based on harmonized data collected in countries encompassing a wide geographical distribution. Risk estimates were adjusted for alcohol consumption and cumulative smoking for oral cancer and oro-hypopharyngeal cancer by time since quitting smoking. Current smokers were used as the reference group, and reduction in risk was reported in a dose-dependent manner, including cessation intervals of ≥ 20 years.]

In addition to the data included in the pooled analysis (Marron et al., 2010), Bosetti et al. (2008) reported RR estimates of oral and pharyngeal cancers combined in former smokers by age at quitting using current smokers as the reference group and using data from two hospital-based case–control studies in Italy. The risk of oral and pharyngeal cancer decreased with quitting smoking irrespective of the age at quitting, and the magnitude of the reduction in risk decreased progressively with lowering of the age at quitting smoking, from OR for quitting at age 55–64 years of 0.48 (95% CI, 0.34–0.66) to OR for quitting at age < 35 years of 0.14 (95% CI, 0.08–0.26). [The Working Group noted that this is the only study

Table 2.17 Cessation of tobacco smoking and risk of oral cancer and/or pharyngeal cancer – case–control studies

Reference Location	Study population, number of participants, study period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/controls	RR or OR (95% CI)	Adjustments/comments
Marron et al. (2010) Central Europe, France, Italy, Switzerland, Latin America, Puerto Rico, USA	Pooled analysis of the INHANCE consortium of 17 hospital-based and population-based case–control studies (including men and women) accruing a total of 3302 oral cancer cases, 3989 oropharyngeal or hypopharyngeal cancer cases, and 16 377 controls. Most cases were diagnosed with SCC	Invasive tumour of the oral cavity, oropharynx, hypopharynx, or oral cavity or pharynx not otherwise specified		Oral cancer:		Former smokers include people who had quit smoking cigarettes, cigars, or pipe for > 1 year as of date of diagnosis or date of interview Risk estimates adjusted for age, sex, race/ethnicity, study centre, education level, pack-years of tobacco smoking, and frequency of alcohol consumption
			Smoking:		meta-OR:	
			Current smokers	2256/5183	1.0 (ref)	
			Former smokers	583/5009	0.30 (0.26–0.34)	
			Duration of cessation (yr):			
			> 1–4	156/620	0.65 (0.52–0.80)	
			5–9	129/836	0.43 (0.32–0.58)	
			10–19	144/1582	0.25 (0.21–0.31)	
			≥ 20	154/1971	0.19 (0.15–0.24)	
			Never-smokers	463/6186	0.19 (0.14–0.27)	
					$P_{trend} < 0.01$	
				Oro/hypopharyngeal cancer:		
			Current smokers	2565/5183	1.0 (ref)	
			Former smokers	957/5009	0.41 (0.32–0.53)	
			Duration of cessation (yr):			
			> 1–4	260/620	0.72 (0.52–1.00)	
			5–9	198/836	0.51 (0.38–0.67)	
			10–19	272/1582	0.36 (0.27–0.49)	
			≥ 20	281/1971	0.29 (0.19–0.43)	
			Never-smokers	467/6186	0.25 (0.15–0.42)	
					$P_{trend} < 0.01$	

Table 2.17 (continued)

Reference Location	Study population, number of participants, study period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/controls	RR or OR (95% CI)	Adjustments/comments
Radoï et al. (2013a) France	Multicentre population-based case–control study of UADT and lung cancer (ICARE) conducted in 10 departments in France with cancer registration (2002–2007), including men and women. Of 968 oral cancer cases contacted, 792 (82%) completed the questionnaire and 772 cases aged ≤ 75 yr were included. Controls were randomly selected from the population by random-digit dialling; 3555 (80.6%) were included	Incident and histology- or cytology-confirmed SCC of the oral cavity including the floor of the mouth, mobile tongue, base of the tongue, soft palate, gums, hard palate, and other parts of the mouth (ICD-10 codes C01–C06)		Oral cancer:		Former smokers were people who had stopped smoking for ≥ 2 yr before the study interview. Current smokers included people who had stopped recently (within < 2 yr of the date of the interview) Estimates adjusted for age, sex, area of residence, pack-years of smoking, (continuous variable), and alcohol consumption (categories of grams per day)
			Any smoking:			
			Never-smokers	62/1262	1.0 (ref)	
			Current smokers	537/820	9.8 (7.0–16.6)	
			Former smokers	171/1464	–	
			Duration of cessation (yr):			
			2–9	90/318	3.9 (2.7–5.9)	
			10–19	42/384	2.1 (1.3–3.3)	
			20–29	22/413	1.3 (0.7–2.2)	
			≥ 30	15/346	1.6 (0.9–3.0)	
De Stefani et al. (2007) Montevideo (Uruguay)	Hospital-based case–control study enrolling study participants (men only) in 4 hospitals (1988–2000), including 335 oral cancer and 441 pharyngeal cancer cases and 1501 controls with non-neoplastic conditions not related to tobacco use or alcohol consumption	Microscopically confirmed SCC of the mouth and pharynx	Smoking:	Oral cancer:		Current smokers include people who smoked at the time of the interview or had quit smoking ≤ 1 yr before the date of the interview. Smokers who had quit > 1 yr before the interview were considered former smokers Estimates adjusted for age, residence, urban/rural status, hospital, year at diagnosis, education level, family history of cancer among first-degree relatives, occupation, total consumption of vegetables and fruits, maté intake, and alcohol consumption. No adjustment for intensity or duration of smoking
			Current smokers	261/639	1.0 (ref)	
			Former smokers, duration of cessation (yr):			
			≤ 9	47/182	0.65 (0.44–0.94)	
			10–19	10/146	0.16 (0.08–0.32)	
			≥ 20	9/160	0.15 (0.07–0.31)	
			Never-smokers	8/374	0.08 (0.04–0.16)	
					$P_{trend} < 0.0001$	
				Pharyngeal cancer:		
			Current smokers	340/639	1.0 (ref)	
			Former smokers, duration of cessation (yr):			
			≤ 9	63/182	0.64 (0.45–0.91)	
			10–19	18/146	0.22 (0.13–0.39)	
			≥ 20	15/160	0.22 (0.12–0.40)	
			Never-smokers	5/374	0.04 (0.01–0.10)	
					$P_{trend} < 0.0001$	

Table 2.17 (continued)

Reference Location	Study population, number of participants, study period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/controls	RR or OR (95% CI)	Adjustments/comments
Lee et al. (2009) Czech Republic, Croatia, France, Germany, Greece, Ireland, Italy, Norway, Spain, and the United Kingdom	Multicentre hospital-based case–control study (ARCAGE) of aerodigestive tract cancer, including men and women, enrolling 993 cases of oral or oropharyngeal cancer and 2221 controls (1987–1992; 2002–2005) with conditions not related to tobacco use or alcohol consumption. In this analysis, 974 cases and 2168 controls were included	Histology- or cytology-confirmed SCC of the oral cavity or the pharynx (excluding the nasopharynx)		Oral and pharyngeal cancer:		Former smokers included people who had stopped smoking ≥ 12 months before enrolment Estimates adjusted for age, sex, education level, centre, and alcohol consumption frequency (continuous) and duration (continuous)
			Any smoking:			
			Never-smokers	109/712	1.0 (ref)	
			Current smokers	660/715	5.83 (4.50–7.54)	
			Former smokers	205/741	1.80 (1.37–2.37)	
			Duration of cessation (yr):			
			< 20 yr, > 0–20 pack-years	40/132	2.13 (1.40–3.25)	
			< 20 yr, > 20 pack-years	106/247	3.05 (2.19–4.25)	
			≥ 20 yr, > 0–20 pack-years	40/263	1.09 (0.73–1.64)	
			≥ 20 yr, > 20 pack-years	19/95	1.49 (0.84–2.63)	
			Current smokers:			
			> 0–20 pack-years	102/219	3.42 (2.45–4.78)	
			21–40 pack-years	257/258	6.65 (4.95–8.93)	
			> 40 pack-years	298/244	8.46 (6.22–11.5)	
					$P_{trend} < 0.001$	
Varela-Lema et al. (2010) Galicia (Spain)	Hospital-based case–control study enrolling men aged > 20 yr with newly diagnosed oral or pharyngeal cancer and controls from consecutive patients to undergo surgery not related to tobacco use or alcohol consumption at the same hospital (1996–2000), including 92 cancer cases and 230 controls	Incident histopathology-confirmed primary oral or pharyngeal cancer (ICD-10 codes C00–C14), excluding the lip		Oral and pharyngeal cancer:		Former smokers defined as people who had quit > 6 months before the date of the study interview Estimates adjusted for age, lifetime tobacco consumption, alcohol consumption in grams per week, high-risk occupation, and education level
			Smoking:			
			Current smokers	73/67	1.0 (ref)	
			Former smokers, duration of cessation (yr):			
			1–10	10/31	0.6 (0.2–1.5)	
			> 10	7/50	0.3 (0.1–0.9)	

Table 2.17 (continued)

Reference Location	Study population, number of participants, study period	Cancer end-point	Smoking and smoking cessation metrics	Number of cases/controls	RR or OR (95% CI)	Adjustments/comments
Bosetti et al. (2008) Milan, Pordenone, Rome (Italy)	Data from 2 multicentre hospital-based case–control studies on UADT cancer conducted in 1984–1997 in northern and central Italy. Analysis shown restricted to enrolled men aged < 75 yr. 961 cases of oral and pharyngeal cancer and 2824 controls included. This study population is included in the INHANCE consortium data set, but analysis by age at quitting is not reported in Marron et al. (2010)	Incident histologically confirmed oral and pharyngeal cancer		Oral and pharyngeal cancer:		Former smokers defined as people who had stopped smoking ≥ 12 months before enrolment and at age < 65 yr Reference group included current smokers and former smokers who had quit at age ≥ 65 yr Estimates adjusted for age, centre, education level, and alcohol consumption
			Smoking:			
			Current smokers	712/1176	1.0 (ref)	
			Former smokers, age at quitting:			
			55–64 yr	75/203	0.48 (0.34–0.66)	
			45–54 yr	90/301	0.36 (0.27–0.48)	
			35–44 yr	45/279	0.20 (0.14–0.29)	
			< 35 yr	13/162	0.14 (0.08–0.26)	

ARCAGE, Alcohol-Related Cancers and Genetic Susceptibility in Europe; CI, confidence interval; ICARE, Investigation of Occupational and Environmental Causes of Respiratory Cancers; ICD, International Classification of Diseases; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio; ref, reference; RR, relative risk; SCC, squamous cell carcinoma; UADT, upper aerodigestive tract; yr, year or years.

identified that documents the impact of age at quitting on the RR reduction.]

Radoï et al. (2013a) reported on a multicentre population-based case–control study (the Investigation of Occupational and Environmental Causes of Respiratory Cancers [ICARE] study) of upper aerodigestive tract cancer, including oral cancer, conducted in 2002–2007 in 10 departments in France with cancer registration, including male and female participants. The ICARE study documented time since quitting smoking in former smokers and used never-smokers as the reference group. The RR of oral cancer in former smokers decreased in magnitude with increasing time since quitting smoking but remained significantly elevated with up to 19 years since quitting (OR for 2–9 years of quitting, 3.9; 95% CI, 2.7–5.9; OR for 10–19 years of quitting, 2.1; 95% CI, 1.3–3.3; OR for 20–29 years of quitting, 1.3; 95% CI, 0.7–2.2; OR for ≥ 30 years of quitting, 1.6; 95% CI, 0.9–3.0) [no trend reported]. The estimates were markedly lower than the RR in current smokers (OR, 9.8; 95% CI, 7.0–16.6). [The Working Group acknowledged the moderate sample size of this study, which used robust definitions of former smoker and current smoker and enrolled participants from a wide geographical distribution in France, and also generated risk estimates adjusted for alcohol consumption and cumulative smoking by time since quitting smoking but used never-smokers as the reference group.]

De Stefani et al. (2007) conducted a male-only hospital-based case–control study assessing the effects of tobacco smoking and alcohol consumption on the occurrence of oral and pharyngeal cancers in Montevideo, Uruguay, in 1988–2000. The risk of oral cancer in former smokers was lower than that in current smokers within 9 years of quitting smoking (OR, 0.65; 95% CI, 0.44–0.94) and decreased markedly with longer time since quitting (OR for 10–19 years of smoking cessation, 0.16; 95% CI, 0.08–0.32; OR for ≥ 20 years of smoking cessation, 0.15, 95% CI, 0.07–0.31). Similarly, the risk of pharyngeal cancer in former smokers was lower than that in current smokers within 9 years of quitting smoking (OR, 0.64; 95% CI, 0.45–0.91) and continued to decrease with longer time since quitting (OR for ≥ 20 years of cessation, 0.22; 95% CI, 0.12–0.40). [The Working Group noted the high participation rates of eligible cases and controls, the generation of fully adjusted risk estimates, including by alcohol consumption, and the use of a definition of former smoker that classified smokers quitting within 1 year of the date of cancer diagnosis or interview as current smokers rather than former smokers, which reduced the possible distortion of risk estimates by exposure misclassification. The Working Group also observed that the ORs for former smokers by time since quitting smoking were not adjusted for intensity, duration, or cumulative past smoking.]

Lee et al. (2009) reported on a multicentre international hospital-based case–control study of aerodigestive tract cancer (the Alcohol-Related Cancers and Genetic Susceptibility in Europe [ARCAGE] study), which collected information on smoking and smoking cessation interval in former smokers. The study enrolled male and female cases and controls in 10 countries (the Czech Republic, Croatia, France, Germany, Greece, Ireland, Italy, Norway, Spain, and the United Kingdom) in 2002–2005 (with the exception of cases and controls in France, recruited earlier). The RR of oral and pharyngeal cancer in former smokers decreased with longer duration of cessation in people with equivalent cumulative pack-years of smoking, and the RR in current smokers with similar smoking history was markedly higher ($P < 0.001$). For instance, for former smokers with > 0 to 20 pack-years of smoking, the ORs were 2.13 (95% CI, 1.40–3.25) for < 20 years of quitting and 1.09 (95% CI, 0.73–1.64) for ≥ 20 years of quitting, compared with an OR of 3.42 (95% CI, 2.45–4.78) in current smokers. The reduction in risk with increasing

time since quitting was observed for both categories of cumulative smoking (0–20 pack-years and > 20 pack-years), but the magnitude of the risk estimates was higher in former smokers with higher cumulative smoking. [The Working Group acknowledged the large size of this multicentre study based on European populations, and the calculation of risk estimates by time since quitting, using two categories of cumulative smoking; however, the study reported RR estimates for oral and pharyngeal cancers combined, precluding the identification of risk of oral cancer alone.]

Varela-Lema et al. (2010) reported on a hospital-based case–control study in Santiago de Compostela, Galicia, Spain, in 1996–2000 investigating the association between tobacco smoking and oral cancer and/or pharyngeal cancer in men. A total of 92 cases and 230 controls were included in the analysis, which combined cases of oral and pharyngeal cancer and considered two categories for time since quitting smoking: 1–10 years and > 10 years. Using current smokers as the reference group, the risk of oral and pharyngeal cancer decreased in former smokers with > 10 years of quitting (OR, 0.3; 95% CI, 0.1–0.9). This study also provided ORs using never-smokers as the reference group, generating very high ORs in former smokers (OR, 4.8; 95% CI, 2.9–73.5) and in current smokers (OR, 34.5; 95% CI, 7.5–157.8), which included light and heavy consumers of alcohol; heavy alcohol consumers were over-represented in current smokers. [Adjustment by alcohol consumption may not have entirely controlled for the risk-potentiating effect of dual exposure to these two risk factors, particularly in current consumers. The Working Group acknowledged the reporting of cancer risk estimates by time since quitting smoking in this small study. However, this study did not include any description of matching of controls to cases, and participation rates in cases and controls were not mentioned. The definition of former smoker included people who had quit smoking for only ≥ 6 months by the time of enrolment, and risk estimates were combined for oral and pharyngeal cancers.]

(b) Risk of OPMDs

See Table 2.18.

(i) Overview of studies

A group of studies, limited in sample size, addressing cessation of tobacco smoking and incidence of OPMDs was available to the Working Group. These included one cohort study (Gupta et al., 1995), six case–control studies (Macigo et al., 1996; Hashibe et al., 2000a, b; Shiu et al., 2000; Fisher et al., 2005; Amarasinghe et al., 2010a; Li et al., 2011), and one cross-sectional study (Pivovar et al., 2017). Most of these studies included male and female participants; two studies were based only on men (Gupta et al., 1995; Pivovar et al., 2017). Most of these studies reported the RR of OPMDs or a specific OPMD (i.e. leukoplakia or erythroplakia) in former smokers using never-smokers as the reference group, and one study described effect estimates by time since quitting smoking (Macigo et al., 1996).

(ii) Intervention study

Gupta et al. (1995) reported on a very large cohort study in Ernakulam District in Kerala, India, with a 10-year follow-up (Table 2.18). Men accrued 77 681 person-years of observation, and women accrued 32 544 person-years of observation. The prevailing risk factors in the study population were bidi smoking and betel quid chewing, along with commercial cigarette smoking. The study calculated age-adjusted incidence rates separately for each type of OPMD, and the ratio of leukoplakia incidence was estimated between former smokers and current smokers. In men, who reported smoking more frequently than women, the age-adjusted incidence of leukoplakia was 24 per 100 000 (1 incident case) in former bidi smokers and 155 per 100 000 (80

Table 2.18 Cessation of tobacco smoking and risk of OPMDs

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Gupta et al. (1995) Kerala, Trivandrum (India) Intervention study	Cohort of 12 212 male and female tobacco users aged ≥ 15 yr identified in a baseline house-to-house survey (1977–1978) and recontacted annually for tobacco control education. Incidence of OPMDs at the 10-yr follow-up visit is reported by tobacco cessation Men accrued 77 681 person-years, and women accrued 32 544 person-years	Leukoplakia	Bidi smoking: Stopped Continued	Men (cases/ age-adjusted incidence): 1/24 per 100 000 80/155 per 100 000	Incidence ratio: 0.15 (N/A) –	Stopping smoking defined as quitting bidi or cigarette smoking for > 6 months at the time of the 10-year survey. Duration of cessation not reported Incidence rates age-adjusted Large sample size of men and women at high risk of developing OPMDs. The proportion of person-years accrued of tobacco cessation was higher in women (14.4%, mainly chewing) than in men (6.5%, mainly bidi smoking). Risk estimates reported without a measure of precision

Table 2.18 (continued)

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Macigo et al. (1995, 1996) Meru District (Kenya)	Community-based case–control study of cases of leukoplakia, including men and women aged 21–75 yr residing for ≥ 5 yr in the Githongo sublocation of Meru District (n = 85), and age-, sex-, and sampling cluster-matched controls (n = 141), including administration of structured questionnaire and oral examination	Clinically diagnosed cases of leukoplakia	Industrial cigarette smoking:	Cases/controls:	Leukoplakia:	Definition of former smoker not provided RRs not adjusted for potential confounders (i.e. alcohol consumption) Well-defined clinical diagnostic criteria and histological confirmation
			Never-smokers	18/78	1.0 (ref)	
			Former smokers	5/31	0.7 (0.2–2.3)	
			Current smokers	62/32	8.4 (4.1–17.4)	
			Kiraiku hand-rolled cigarette smoking:			
			Never-smokers	42/120	1.0 (ref)	
			Former smokers	29/17	4.9 (2.3–10.4)	
			Current smokers	14/4	10.0 (2.9–43.4)	
			Time smoking before quitting (yr):			
			≤ 10	24/15	4.6 (2.1–10.2)	
			> 10	5/2	7.1 (1.1–76.6)	
			Duration of cessation (yr):			
			≤ 4	6/2	8.6 (1.4–88.7)	
			5–9	12/7	4.9 (1.7–14.9)	
			≥ 10	11/8	3.9 (1.4–11.6)	

Table 2.18 (continued)

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Hashibe et al. (2000a, b) Kerala (India)	Community-based case–control study nested in an intervention trial screening male and female residents aged ≥ 35 yr and identifying 49 174 eligible study participants examined at home. 3585 people with suspicious OPMDs or cancer lesions referred to the dentist or the oncologist. The study included 927 cases of leukoplakia, 100 cases of erythroplakia, and 47 773 controls	Leukoplakia or erythroplakia diagnosed by a dentist	Tobacco smoking: Never-smokers Former smokers Occasional smokers Current smokers Never-smokers Former smokers Current smokers, 1–20×/day Current smokers, 21–40×/day	Cases/controls: 428/35 591 46/1815 19/764 434/9602 428/35 591 NR NR NR	Leukoplakia: 1.0 (ref) 1.7 (1.0–2.7) 2.0 (1.4–2.8) 3.4 (2.8–4.1) Erythroplakia: 1.0 (ref) 1.6 (0.8–2.9) 1.2 (0.6–2.4) 2.3 (1.1–5.1)	Former smoker not defined, and duration of smoking cessation not reported Former smoking-associated leukoplakia and erythroplakia effect estimates adjusted for age, sex, education level, BMI, years of chewing, and years of alcohol consumption Large sample size, leukoplakia lesions confirmed by a dentist, and effect estimates fully adjusted for important confounders
Shiu et al. (2000) Taiwan (China)	Hospital-based case–control study of 100 randomly selected cases of leukoplakia out of a cohort of 580 patients with leukoplakia diagnosed at a single institution in 1988–1998, and 100 age-, sex-, and date of diagnosis-matched controls randomly selected from patients diagnosed with periodontal disease at the same hospital	Cohort of leukoplakia cases clinically diagnosed according to WHO definition	Cigarette smoking: Never-smokers Former smokers Current smokers	Cases/controls: NR NR NR	Leukoplakia: 1.0 (ref) 1.04 (0.24–4.59) 3.22 (1.06–9.78)	Former smoker not defined, and duration of smoking cessation not reported ORs adjusted for alcohol consumption and areca nut chewing Effect estimates are adjusted for important confounders. Incomplete reporting, and estimates with low precision

Table 2.18 (continued)

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Fisher et al. (2005) West Virginia (USA)	Community-based case–control study of cases (n = 90) identified at a leukoplakia tissue registry and controls (n = 78) at the surgical biopsy service supporting the tissue registry but with a diagnosis of periapical cyst (ICD-9 code 522.8) and no diagnosis of leukoplakia	Leukoplakia histologically confirmed as ICD-9 code 528.6 with hyperkeratosis with or without epithelial atypia or dysplasia	Tobacco smoking: Never-smokers Former smokers Current smokers	Cases/controls: 38/25 30/29 22/24	Leukoplakia:* 1.0 (ref) 0.71 (0.27–1.86) 0.48 (0.17–1.33)	Former smoker not defined, and duration of smoking cessation not reported. Leukoplakia ORs adjusted for age, sex, smokeless tobacco use, daily alcohol consumption, and dental prostheses use. [*Results shown correspond to model assessing smokeless tobacco use] Cases with histological confirmation, and effect estimates fully adjusted, but small sample size
Amarasinghe et al. (2010a) Sabaragamuwa Province (Sri Lanka)	Community-based case–control study built on a randomly selected multistage cross-sectional sample (n = 1029) of people aged > 30 yr drawn to assess the prevalence of OPMDs in a rural setting. People with suspected OPMDs on oral examination were considered cases (n = 102), and screenees free of oral mucosa abnormalities were considered controls	Suspected cases of leukoplakia identified during screening referred to the hospital for histopathological confirmation	Tobacco smoking: Never-smokers Former smokers Occasional smokers Current smokers	Cases/controls: 43/NR 6/NR 6/NR 15/NR	Leukoplakia: 1.0 (ref) 0.5 (0.2–1.6) 0.8 (0.3–2.5) 0.7 (0.3–1.6)	Former smokers included ever-smokers who had quit > 1 calendar year before the date of diagnosis or interview Smoking-related effect estimates adjusted for sex, age, education level, BMI, occupation, β-carotene-containing total fruit and vegetable portions, betel quid chewing, and alcohol consumption Cases with histological confirmation, and risk estimates fully adjusted, but incomplete exposure reporting and small number of exposed cases. Study in a population where chewing is common

Table 2.18 (continued)

Reference Location	Study design and population	End-point	Exposure category	Number of study participants/ cases/controls/ age-adjusted incidence	Risk estimate/ prevalence or incidence ratio (95% CI)	Adjustments/comments
Li et al. (2011) Puerto Rico (USA)	Case–control study identifying men and women aged ≥ 30 yr with an oral cavity examination histopathology report generated in 2003–2007 at pathology laboratories in Puerto Rico. People with benign oral lesions (n = 155) were considered controls, and those with OPMDs (n = 86) were considered cases	Histopathological diagnosis of oral hyperkeratosis, epithelial hyperplasia, and epithelial dysplasia in people with no prior history of oral lesions	Tobacco smoking: Never-smokers Former smokers Current smokers	Cases/controls with benign lesions: 38/99 17/30 31/26	OPMD, OR: 1.0 (ref) 1.47 (0.67–3.21) 4.32 (1.99–9.38)	Former smoker defined as a person who was an ever-smoker and quit smoking for > 1 calendar year before the year of diagnosis. No information on duration of cessation was reported Estimates adjusted for age, sex, education level, fruit and vegetable intake, and alcohol consumption (4 levels) Cases histologically confirmed, and interviewer blinded on case–control status of responders. Original specific OPMDs in cases not reported
Pivovar et al. (2017) Curitiba, Paraná (Brazil)	Cross-sectional study to screen for oral cancer in high-risk men (former or current smokers) aged 50–65 yr registered in a primary health-care programme; 233 were ever-smokers, and 202 completed the oral examination at the dentist	OPMDs and oral cancer first diagnosed by a dentist on clinical grounds and suspected lesions with histological analysis.	Tobacco smoking: Former smokers Current smokers Leukoplakia: Former smokers Current smokers	Screened OPMD-positive/ negative: 13/76 44/69 6/83 34/79	Prevalence ratio: 1.0 (ref) 2.66 (NR) 1.0 (ref) 4.31 (1.76–10.57)	Former smokers included ever-smokers with a smoking history of ≥ 20 yr and who had quit < 5 yr before the interview. Model generating leukoplakia prevalence ratios in current smokers to former smokers adjusted for family income and history of compliance with clinical examinations Histological confirmation. No adjustment for alcohol consumption

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; N/A, not available; NR, not reported; OPMDs, oral potentially malignant disorders; OR, odds ratio; ref, reference; RR, relative risk; WHO, World Health Organization; yr, year or years.

incident cases) in current bidi smokers, generating an incidence ratio of 0.15. [The Working Group noted that although the incidence ratio was reported without an estimate of precision and without taking alcohol consumption into account, such a large decrease in the incidence of leukoplakia after quitting bidi smoking, in a population known to have low or no alcohol consumption, is probably not due to chance or confounding.]

(iii) Case–control studies

One hospital-based case–control study (Shiu et al., 2000) and five community-based case–control studies (Macigo et al., 1996; Hashibe et al., 2000a, b; Fisher et al., 2005; Amarasinghe et al., 2010a; Li et al., 2011) were identified, including participants from India, Kenya, Puerto Rico, Sri Lanka, Taiwan (China), and the USA (Table 2.18).

In a community-based case–control study in Meru District in north-eastern Kenya, 85 leukoplakia cases and 141 controls were identified in a house-to-house survey of eligible residents (Macigo et al., 1995, 1996). The RR of leukoplakia in former smokers of commercial cigarettes compared with never-smokers was < 1 (OR, 0.7; 95% CI, 0.2–2.3); this estimate is substantially lower than that in current smokers (OR, 8.4; 95% CI, 4.1–17.4). In contrast, the RR of leukoplakia in former smokers of *kiraiku* hand-rolled cigarettes compared with never-smokers was markedly elevated (OR, 4.9; 95% CI, 2.3–10.4) but was lower than the RR in current smokers of *kiraiku* cigarettes (OR, 10.0; 95% CI, 2.9–43.4). The risk of leukoplakia remained elevated in former smokers with > 10 years of *kiraiku* smoking cessation (OR, 3.9; 95% CI, 1.4–11.6). [The Working Group noted the omission of definitions of former smoker and current smoker. Furthermore, effect estimates associated with smoking were not adjusted for important confounders, including alcohol consumption, a behaviour that is socially accepted in Kenya.]

Hashibe et al. (2000a) reported on a large community-based case–control study embedded in a randomized intervention trial in Kerala, India, screening for oral cancer in male and female residents. The study included 927 cases of leukoplakia confirmed by a dentist and 47 773 screened people free of oral diseases (controls). The RR of leukoplakia in former smokers compared with never-smokers (OR, 1.7; 95% CI, 1.0–2.7) was lower than that in current smokers (OR, 3.4; 95% CI, 2.8–4.2); the effect estimates were controlled for important confounders. In a related publication from the same population (Hashibe et al., 2000b), the association between cigarette smoking and erythroplakia was investigated (100 cases). The RR of erythroplakia in former cigarette smokers compared with never-smokers (OR, 1.6; 95% CI, 0.8–2.9) was lower than the RR in current smokers who reported smoking 21–40 times per day (OR, 2.3; 95% CI, 1.1–5.1) but not lower than the RR in current smokers who reported smoking 1–20 times per day (OR, 1.2; 95% CI, 0.6–2.4). [The Working Group noted that the studies did not provide definitions of former smoker or current smoker and did not present leukoplakia or erythroplakia effect estimates by number of years since quitting smoking.]

Shiu et al. (2000) randomly selected 100 cases of leukoplakia in a cohort of 435 cases diagnosed in 1988–1998 at a medical institution in Taiwan (China) and 100 matched controls. Leukoplakia risk estimates were calculated using never-smokers as the reference group. Multivariate analysis adjusting for alcohol intake and betel quid chewing generated RR estimates in former smokers (OR, 1.04; 95% CI, 0.24–4.59) of lower magnitude than the RR estimates in current smokers (OR, 3.22; 95% CI, 1.06–9.78). [The Working Group noted that the study did not provide definitions of former smoker and current smoker and did not present effect estimates by number of years since quitting smoking.]

Fisher et al. (2005) reported on a case–control study in West Virginia (USA) including cases

of leukoplakia (n = 90; response rate of eligible people, 55%) and controls with a periapical cyst (n = 78; response rate of eligible people, 50%) identified at the same tissue registry in 2001–2002. The fully adjusted RRs of leukoplakia in former smokers (OR, 0.71; 95% CI, 0.27–1.86) and in current smokers (OR, 0.48; 95% CI, 0.17–1.33) were < 1. [The Working Group noted the very modest response rate in cases and in controls, which raises concerns of selection bias. Furthermore, the Working Group acknowledged the omission of a definition of former smoker and the use of a control group with a pathology condition that was not described in any detail; this control group was probably not appropriate. Also, cases and controls differed by socioeconomic status or by education level, factors that were not taken into account and that may influence the level of smoking. Finally, the restriction of controls to people with a periapical cyst may have indirectly selected for controls with prevalent smoking.]

The very small study by Amarasinghe et al. (2010a) included few cases, and all ORs were < 1; it was considered uninformative.

The community-based case–control study of Li et al. (2011) identified men and women aged ≥ 30 years with an oral cavity examination histopathology report generated in 2003–2007 at pathology laboratories in Puerto Rico and lacking a previous history of oral diseases. People with benign oral conditions (n = 155) were considered controls, and those with OPMDs (n = 86), defined as oral epithelial dysplasia, oral hyperkeratosis, or epithelial hyperplasia without epithelial dysplasia, were considered cases. The effect estimate for OPMDs in former smokers compared with never-smokers (OR, 1.47; 95% CI, 0.67–3.21) was lower than that for current smokers compared with never-smokers (OR, 4.32; 95% CI, 1.99–9.38). [The Working Group noted that this case–control study, which clearly defined former smoker, was the only study that defined OPMDs by histopathology features, rather than by clinical entity or diagnosis, so that the dysplasia observed microscopically may have emerged from leukoplakia or from erythroplakia originally detected in the mouth.]

(iv) Cross-sectional studies

Pivovar et al. (2017) reported on a cross-sectional study within the framework of oral cancer screening in primary health care in the city of Curitiba in the state of Paraná in southern Brazil. The prevalence of OPMDs and leukoplakia in former smokers and current smokers was adjusted for family income and history of compliance with clinical examinations. The prevalence of leukoplakia was markedly higher in current smokers than in former smokers (prevalence ratio, 4.31; 95% CI, 1.76–10.57) (Table 2.18). [The Working Group noted that this study compared former smokers with current smokers but calculated the leukoplakia prevalence ratio using former smokers rather than current smokers as the reference group.]

2.3.2 Alcohol consumption

This section summarizes the findings from observational case–control studies, cohort studies, and a pooled analysis that investigated the effect of cessation of alcohol consumption and duration of alcohol cessation on the risks of oral cancer and OPMDs. These included the pooled analysis from the INHANCE consortium with data from 13 case–control studies (Marron et al., 2010), three cohort studies (Ide et al., 2008; Cancela et al., 2009; Im et al., 2021), and two individual case–control studies, one published before the INHANCE analysis (Takezaki et al., 1996) and one published since the INHANCE analysis (Andrade et al., 2015).

(a) Risk of oral cancer

See Table 2.19.

The INHANCE Consortium investigated the effects of quitting alcohol consumption on the

Table 2.19 Cessation of alcoholic beverage consumption and risk of oral cancer and/or pharyngeal cancer

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Pooled analysis of case–control studies						
Marron et al. (2010) International (multiple studies in (France, Italy Switzerland, Latin/Central America, USA)	INHANCE consortium pooled analysis of case–control studies, including men and women; 2615 oral cancer cases, 3989 oropharyngeal or hypopharyngeal cancer cases, and 12 359 and 12 593 controls, respectively (~1990s to early 2000s)	Invasive tumour of the oral cavity, oropharynx, hypopharynx, or oral cavity or pharynx not otherwise specified		Oral cancer:		Former drinkers were defined as people who had quit drinking the following alcoholic beverages: wine, beer, liquor, and aperitifs. People who had stopped drinking for > 1 yr were classified as former drinkers. The number of years that former drinkers had quit drinking was determined from age at reference date (interview or diagnosis date) and age at which they had stopped drinking Analysis adjusted for age, sex, race/ethnicity, study centre, education level, and pack-years of tobacco smoking
			Current drinkers	1131/5715	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	132/504	0.81 (0.61–1.07)	
			5–9	149/576	0.77 (0.52–1.15)	
			10–19	174/801	0.66 (0.47–0.92)	
			≥ 20	155/763	0.45 (0.26–0.78)	
			Never-drinkers	737/3674	0.65 (0.36–1.16)	
					P_{trend} = 0.05	
			< 1 drink/day:			
			Current drinkers	256/2250	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	30/144	1.51 (0.80–2.87)	
			5–9	22/204	1.06 (0.39–2.88)	
			10–19	40/307	0.80 (0.37–1.75)	
			≥ 20	57/338	0.98 (0.54–1.77)	
			Never-drinkers	727/3238	0.86 (0.39–1.89)	
			1–2 drinks/day:			
			Current drinkers	234/1539	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	24/149	0.67 (0.33–1.35)	
			5–9	36/154	1.22 (0.43–3.43)	
			10–19	30/205	0.34 (0.15–0.80)	
			≥ 20	29/186	0.59 (0.22–1.57)	
			Never-drinkers	717/3144	0.58 (0.26–1.28)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Marron et al. (2010) (cont.)			≥ 3 drinks/day:			
			Current drinkers	589/1554	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	77/206	0.79 (0.54–1.14)	
			5–9	90/207	0.85 (0.51–1.41)	
			10–19	102/279	0.82 (0.50–1.34)	
			≥ 20	69/232	0.43 (0.28–0.67)	
			Never-drinkers	727/3580	0.19 (0.09–0.39)	
					P_{trend} = 0.06	
				Oro/hypopharyngeal cancer:		
			Alcohol cessation:			
			Current drinkers	1703/5915	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	213/505	1.04 (0.73–1.48)	
			5–9	240/576	0.95 (0.61–1.49)	
			10–19	340/802	1.15 (0.92–1.43)	
			≥ 20	221/763	0.74 (0.50–1.09)	
			Never-drinkers	406/3693	0.65 (0.42–1.02)	
					P_{trend} = 0.18	
			< 1 drink/day:			
			Current drinkers	338/2444	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	29/144	2.02 (1.07–3.80)	
			5–9	28/205	1.44 (0.65–3.16)	
			10–19	67/309	1.49 (0.96–2.34)	
			≥ 20	60/338	1.16 (0.65–2.05)	
			Never-drinkers	406/3693	0.97 (0.59–1.58)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Marron et al. (2010) (cont.)			1–2 drinks/day:			
			Current drinkers	335/1808	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	38/152	1.09 (0.65–1.82)	
			5–9	33/156	1.09 (0.55–2.16)	
			10–19	55/205	1.06 (0.67–1.68)	
			≥ 20	45/186	0.80 (0.47–1.37)	
			Never-drinkers	400/3599	0.49 (0.30–0.81)	
			≥ 3 drinks/day:			
			Current drinkers	926/1554	1.0 (ref)	
			Duration of cessation (yr):			
			> 1–4	141/206	1.05 (0.69–1.59)	
			5–9	174/207	1.12 (0.60–2.08)	
			10–19	213/279	1.15 (0.73–1.81)	
			≥ 20	115/232	0.77 (0.45–1.30)	
			Never-drinkers	397/3580	0.19 (0.10–0.37)	
					$P_{trend} < 0.01$	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Case–control studies						
Huang et al. (2017) Taiwan (China)	Hospital-based case–control study, including men and women; 509 oral cancer cases, 118 oropharynx cases, and 89 hypopharynx cases (2010–2016)	ICD-classified primary pathologically confirmed squamous cell carcinoma of the oral cavity		Oral cancer:		Age, sex, education, cigarette smoking (pack-year categories), and betel quid chewing (pack-year categories) Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol use No adjustment for past amount of alcohol consumed or duration of smoking cessation
			Non-drinkers (never + occasional)	195/517	1.0 (ref)	
			Former drinkers	61/109	0.77 (0.51–1.17)	
			Current drinkers	253/314	1.29 (0.97–1.73)	
				Oropharyngeal cancer:		
			Non-drinkers (never + occasional)	29/517	1.0 (ref)	
			Former drinkers	20/109	2.83 (1.39–5.76)	
			Current drinkers	69/314	4.23 (2.38–7.52)	
				Hypopharyngeal cancer:		
			Non-drinkers (never + occasional)	4/517	1.0 (ref)	
			Former drinkers	19/109	14.02 (4.38–44.85)	
			Current drinkers	66/314	21.55 (7.36–63.15)	
Andrade et al. (2015) Brazil	Hospital-based case–control study, with data abstracted from medical records, including men and women; 127 oral cancer cases and 381 controls (2002–2012)	Histopathologically confirmed oral squamous cell carcinoma		Oral cancer:		Moderate-sized case–control study Alcohol consumption categories not defined Crude ORs, no adjustment
			Non-drinkers	27/113	1.0 (ref)	
			Former drinkers	56/57	2.73 (1.73–4.31)	
			Current drinkers	44/84	1.07 (0.69–1.68)	
			Duration of cessation (yr):			
			≥ 10	20/41	1.0 (ref)	
			< 10	36/16	4.61 (2.08–10.22)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
De Stefani et al. (2007) Uruguay	Hospital-based case–control study, including men only; 335 oral cancer cases and 441 pharyngeal cancer cases (1998–2000)	Microscopically confirmed squamous cell carcinoma of the mouth or pharynx		Oral cancer:		Adjusted for age, residence, urban/rural status, hospital, diagnosis year, education, first-degree family history of cancer, total vegetable and fruit, and maté intake, occupation, smoking status, years since quitting smoking and current cigarettes/day Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol use No adjustment for past amount of alcohol consumed
			Non-drinkers	34/527	1.0 (ref)	
			Former drinkers	91/317	3.0 (1.9-4.7)	
			Current drinkers	210/657	3.4 (2.3-5.2)	
				Pharyngeal cancer:		
			Non-drinkers	33/527	1.0 (ref)	
			Former drinkers	116/317	3.9 (2.5-6.1)	
			Current drinkers	292/657	4.5 (3.0-6.8)	
Zheng et al. (1997) China	Hospital-based case–control study, including men and women; 111 tongue cancer and 111 sex- and age-matched controls (1988–1989)	Histologically confirmed tongue cancer		Tongue cancer:		Adjusted for tobacco, years of education and matching factors Selection of hospital-based controls with conditions thought to be unrelated to smoking or alcohol use No adjustment for past amount of alcohol consumed or duration of smoking cessation
			Non-drinkers	64/72	1.0 (Ref.)	
			Former drinkers	7/6	1.20 (0.58–2.50)	
			Current drinkers	40/33	0.94 (0.28–3.22)	
Takezaki et al. (1996) Japan	Hospital-based case–control study, including men and women; 203 oral cancer cases, 35 oropharyngeal cancer cases, and 28 hypopharyngeal cancer cases	Histologically confirmed, ICD-classified primary oral cancer, oropharyngeal cancer, and hypopharyngeal cancer		Oral, oropharyngeal, and hypopharyngeal cancer:		Alcohol consumption defined and standardized Crude ORs, no adjustment Not clear what reference group is – possibly never-drinkers
			Duration of cessation (yr):			
			0 (never quit)	138/13 811	1.2 (0.9–1.6)	
			0–4	9/320	2.4 (1.1–5.1)	
			5–14	4/180	1.7 (0.6–4.8)	
			≥ 15	4/62	3.4 (1.2–9.9)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Ko et al. (1995) Taiwan (China)	Hospital-based case–control study, including men and women; 107 oral cancer cases and 200 controls (1992–1993)	Histologically confirmed, ICD-classified oral cancer,		Oral cancer:		Adjusted for education, occupation, cigarette smoking and betel chewing status No details on selection of hospital-based controls provided No adjustment for past amount of alcohol consumed or duration of smoking cessation
			Non-drinkers	25/89	1.0 (ref)	
			Former drinkers	14/37	1.0 (0.3–3.3)	
			Current drinkers	68/74	2.2 (1.0–4.9)	
Cohort studies						
Im et al. (2021) China	Cohort study. 209 237 men, aged 30–79 years, with no previous history of cancer; follow-up time from 2004 until January 2017 (median 10 years); incident cancer cases ascertained by linkage with cancer registries and the National Health insurance databases	Cancer of mouth or throat by ICD-10 codes (C00-C14, C32)		Mouth or throat cancer incidence:		Analysis adjusted for age, study area, education, income, smoking, physical activity, fruit intake, BMI, and family history of cancer Floating standard errors were used to estimate the confidence intervals Abstention is the reference category No adjustment for past amount of alcohol consumed or duration of smoking cessation No data on alcohol and oral cancer risk among women provided
			Abstention	23/42 479	1.00 (0.65–1.53)	
			Ex-regular drinkers	12/18 061	1.06 (0.60–1.87)	
			Occasional drinkers	39/78 963	1.33 (0.96–1.86)	
			Current regular drinkers	66/69 734	1.89 (1.46–2.45)	

Table 2.19 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/comments
Cancela et al. (2009) India	Cohort study. Trivandrum Oral Cancer Screening Study RCT, with cancer registry follow-up of incidence and mortality, including men and women aged 35–100 yr; 32 347 participants recruited in 1996. In 10 yr of follow-up (1996–2006), 134 oral cancer cases were diagnosed, and 91 oral cancer deaths were registered	Oral cancer was defined by ICD-10 codes C02 (other and unspecified parts of the tongue), C03 (gum), C04 (floor of the mouth), C05 (palate), and C06 (other and unspecified parts of the mouth)		Oral cancer:		Small numbers of cases and deaths, and consequently wide CIs Individuals who had never consumed alcohol during their lifetime were categorized as never, those who were currently consuming alcohol or those who had stopped drinking alcohol for < 6 months were categorized as current, and those who had quit drinking ≥ 6 months before the time of the interview were categorized as former Analyses adjusted for age, education level, religion, occupation, standard of living, betel quid chewing habits, smoking habits, intake of vegetables, and intake of fruits
				Incidence (person-years):	HR:	
			Never-drinkers	61/178 932	1.00 (ref)	
			Current drinkers	52/85 022	1.49 (1.01–2.21)	
			Former drinkers	21/19 127	1.90 (1.13–3.18)	
				Mortality (person-years):		
			Never-drinkers	43/179 134	1.00 (ref)	
			Current drinkers	34/85 158	1.76 (1.08–2.86)	
			Former drinkers	14/19 212	2.04 (1.08–3.86)	
Ide et al. (2008) Japan	Cohort study. 110 792 participants, including men (46 465) and women (64 327) aged 40–79 yr, recruited in 1988–1990. In 12.5 yr of follow-up, 52 deaths: 25 from oral cancer and 27 from pharyngeal cancer	Oral and pharyngeal cancer deaths were identified by ICD-10 codes C01–C14, excluding C07–C08 (salivary gland cancer) and C11 (nasopharyngeal cancer)	Men:	Oral and pharyngeal cancer mortality:		Non-drinker and former drinker were not defined Small numbers and wide CIs Adjusted for age (continuous), smoking status (never, former, current), consumption of green tea (≥ 1 cups per day, < 1 cup per day, unknown), preference for salty foods (like, normal or dislike, unknown), and consumption of green and yellow vegetables (daily or not)
			Non-drinkers	5/77 513	1.0 (ref)	
			Former drinkers	2/23 423	1.2 (0.2–6.0)	
			Current drinkers	34/319 502	2.0 (0.8–5.1)	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio; RCT, randomized controlled trial; ref, reference; yr, year or years.

risks of oral cancer (based on 12 studies) and oropharyngeal and hypopharyngeal cancers (based on 13 studies) by performing a robust pooled analysis with comprehensive adjustment for confounding factors (Marron et al., 2010). Cessation of alcohol consumption was associated with a reduced risk of oral cancer (OR, 0.60; 95% CI, 0.43–0.84). The reduction in risk after alcohol cessation increases with duration of cessation, with the risk decreasing by > 50% by 20 years of quitting for oral cancer (OR, 0.45; 95% CI, 0.26–0.78) and by about 25% by 20 years of quitting for oropharyngeal and hypopharyngeal cancers combined (OR, 0.74; 95% CI, 0.50–1.09). Further subgroup analyses showed that the effects of quitting on the risk of oral cancer were more pronounced in former heavy drinkers (≥ 3 drinks per day) and the RR reduction became significant after ≥ 20 years of quitting (OR, 0.43; 95% CI, 0.28–0.67); there was no relationship with duration of consumption. For oropharyngeal and hypopharyngeal cancers, the relationship with previous frequency of alcohol consumption and duration of quitting was less clear.

Three cohort studies analysed the risk associated with former alcohol consumption [none of them reported duration of alcohol cessation]. In a cohort in India, former drinkers had a higher risk of oral cancer incidence and death than current drinkers relative to never-drinkers (Cancela et al., 2009). [This study had small numbers of cases and deaths, well-defined categories of alcohol consumption, and robust analyses.] In a cohort in Japan, the RR of oral and pharyngeal cancer death associated with former drinking relative to non-drinking in men was lower than the RR in current drinkers (Ide et al., 2008). [This study had small numbers of deaths. No categories of alcohol consumption were defined, but the analyses were adjusted for potential confounders.] In a recent cohort study of men in China, former drinkers relative to never-drinkers had a lower RR for lip and oral cavity cancer than current drinkers relative to never-drinkers (Im et al., 2021). [This relatively small cohort study did not adjust for past alcohol consumption or smoking in the analysis.]

The individual case–control study published before the INHANCE analysis (Takezaki et al., 1996) showed an increase in risk associated with long duration of quitting (OR for > 15 years of quitting, 3.4; 95% CI, 1.2–9.9). [The numbers of participants in each category were very small, and the estimates were not adjusted for potential confounders, including smoking.] More recently, a small hospital-based case–control study in Brazil (Andrade et al., 2015) reported that cessation of alcohol consumption for < 10 years compared with cessation for ≥ 10 years conferred a large increased risk (OR, 4.61; 95% CI, 2.08–10.22). [The categories of alcohol consumption were not defined, and the crude estimates were not adjusted for any potential confounding factors.]

In addition, four other hospital-based case–control studies (Ko et al., 1995; Zheng et al., 1997; De Stefani et al., 2007; Huang et al., 2017) reported only risks associated with former drinking relative to never drinking. In all four studies, the risk associations for former drinking relative to never drinking were lower than those for current drinking relative to never drinking; ORs ranged from 0.77 to 3.0 for former drinking and from 1.2 to 3.4 for current drinking (relative to never drinking).

(b) Risk of OPMDs

See Table 2.20.

No studies were identified that showed the effect of duration of alcohol cessation on the risk of OPMDs. Seven case–control studies reported risk estimates for former drinkers relative to never-drinkers alongside estimates for current drinkers relative to never-drinkers. [The studies generally had small sample sizes and were of varying quality.] Two studies reported OPMD outcomes combined, one reported multiple

Table 2.20 Cessation of alcoholic beverage consumption and risk of OPMDs

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/ comments
Case–control studies						
Li et al. (2011) Puerto Rico (USA)	Case–control study, including men and women aged ≥ 30 yr. People with benign oral lesions (n = 155) were considered controls, and those with OPMDs (n = 86) were considered cases (2003–2007)	Histopathological diagnosis of oral hyperkeratosis, epithelial hyperplasia, and epithelial dysplasia in people with no prior history of oral lesions		OPMDs:		Never-drinker and former drinker not defined. Small numbers and wide CIs Adjusted for age (4 levels), sex, education level (3 levels), fruit and vegetable intake (4 levels), and current smoking
			Never-drinkers	41/73	1.0 (ref)	
			Ever-drinkers	45/82	0.63 (0.33–1.21)	
			Former drinkers	14/22	0.63 (0.25–1.57)	
			Current drinkers	31/60	0.63 (0.32–1.26)	
Amarasinghe et al. (2010a) Sri Lanka	Community-based case–control study. Randomly selected multistage cross-sectional sample (n = 1029) including men and women aged > 30 yr. People with suspected OPMDs on oral examination were considered cases (n = 102), and screenees free of oral mucosa abnormalities were considered controls	Suspected cases of leukoplakia identified during screening referred to the hospital for histopathological confirmation		OPMDs:		Former drinkers also include current occasional drinkers Adjusted for sex, age, socioeconomic status, β-carotene-containing fruits and vegetables portion, BMI, smoking, betel quid chewing, and alcohol consumption
			Non-drinkers	39/551	1.0 (ref)	
			Monthly, weekly, and daily drinkers	27/114	2.7 (1.2–6.3)	
			Former, occasional drinkers	35/63	1.1 (0.5–2.6)	
Lee et al. (2003) Taiwan (China)	Community-based case–control study, including men and women aged ≥ 15 yr. Cases of leukoplakia or OSF (1994 and 1995). 219 OPMD cases and 876 age- and sex-matched controls were enrolled	Leukoplakia or OSF. Histologically confirmed and diagnosed according to WHO definitions		Leukoplakia:		Adjusted for education level and occupation
			Never-drinkers	72/349	1.0 (ref)	
			Former drinkers	9/40	1.1 (0.5–2.4)	
			Current drinkers	44/111	1.8 (1.1–2.8)	
				OSF:		
			Never-drinkers	55/266	1.0 (ref)	
			Former drinkers	7/27	1.4 (0.6–3.4)	
			Current drinkers	32/83	1.8 (1.1–3.1)	

Table 2.20 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/ comments
Thomas et al. (2003) India	Community-based case–control study nested in an intervention trial screening men and women aged ≥ 35 yr and identifying 49 174 eligible study participants examined at home. 3585 people with suspicious OPMDs or cancer lesions referred to the dentist or the oncologist. The study included 927 cases of leukoplakia, 100 cases of erythroplakia, 115 people with multiple OPMDs, and 47 773 controls	Multiple OPMDs diagnosed by a dentist		Multiple OPMDs:		Large sample size. Confirmed diagnosis by dentist Adjusted for age, sex, education level, BMI, smoking (continuous, pack-years), tobacco chewing (continuous, duration in years), fruit intake (low or high), and vegetable intake (low or high)
			Non-drinkers	91/40 801	1.0 (ref)	
			Occasional drinkers	4/2743	1.1 (0.4–3.2)	
			Current drinkers	13/2754	1.3 (0.6–3.0)	
			Former drinkers	7/1475	1.8 (0.7–4.5)	
Hashibe et al. (2000a) India	Community-based case–control study described above in Thomas et al. (2003)	Leukoplakia diagnosed by a dentist		Leukoplakia:		Large sample size. Confirmed diagnosis by dentist Adjusted for age, sex, education level, BMI, smoking, and tobacco chewing
			Non-drinkers	619/40 801	1.0 (ref)	
			Occasional drinkers	65/2743	1.2 (0.9–1.6)	
			Current drinkers	165/2754	1.6 (1.2–2.0)	
			Former drinkers	78/1475	1.4 (1.1–1.9)	
Hashibe et al. (2000b) India	Community-based case–control study described above in Thomas et al. (2003)	Erythroplakia diagnosed by a dentist		Erythroplakia:		Large sample size. Confirmed diagnosis by dentist Adjusted for age, sex, education level, BMI, smoking (continuous, pack-years), and chewing tobacco (continuous, duration in years)
			Non-drinkers	62/40 801	1.0 (ref)	
			Occasional drinkers	3/2743	0.9 (0.3–3.1)	
			Current drinkers	21/2754	5.8 (2.7–12.5)	
			Former drinkers	14/1475	4.8 (2.4–9.7)	

Table 2.20 (continued)

Reference Location	Study population, number of participants, study period	Oral cancer or precancer end-point	Exposure category	Number of cases/controls	OR (95% CI)	Adjustments/ comments
Macigo et al. (1996) Kenya	Community-based case–control study of cases of leukoplakia, including men and women aged 21–75 yr residing for ≥ 5 yr in the Githongo sublocation of Meru District (n = 85), and age-, sex-, and sampling cluster-matched controls (n = 141), including administration of structured questionnaire and oral examination	Clinically diagnosed cases of leukoplakia (147 lesions in 85 cases). Only 5 cases had non-homogeneous lesions. Biopsies obtained in 49 cases, and histopathology examination revealed no cancer and 11 cases of moderate to severe dysplasia		Leukoplakia:		Alcohol consumption not defined RRs not adjusted for potential confounders (i.e. alcohol consumption) Crude estimates, not adjusted for potential confounders
			Never-drinkers	26/62	1.0 (ref)	
			Current drinkers	39/47	2.0 (1.0–3.9)	
			Former drinkers	36/49	1.5 (0.7–3.3)	

BMI, body mass index; CI, confidence interval; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; ref, reference; RR, relative risk; WHO, World Health Organization; yr, year or years.

OPMDs, three reported leukoplakia, one reported erythroplakia, and one reported OSF. Relative to never-drinkers, the RR estimates for OPMDs were generally (in 4 of 7 studies) lower in former drinkers than in current drinkers, for former drinkers ranging from 1.1 to 1.8 and for current drinkers ranging from 1.3 to 2.7. In the three studies that reported leukoplakia outcomes, the risk estimates in former drinkers compared with never-drinkers ranged from 1.1 to 1.5 and those in current drinkers compared with never-drinkers ranged from 1.6 to 2.0; however, the CIs were wide and overlapping.

2.3.3 Smokeless tobacco use

(a) Risk of oral cancer

Six informative observational studies that reported on the association between former use of smokeless tobacco and risk of oral cancer, including two cohort studies and four case–control studies, were identified by the Working Group. In most of these studies, the former use category was defined at study entry, and often no information was provided with respect to duration of cessation. Studies were well powered with sufficient sample size to estimate overall effects but tended to have small numbers of former users. There were no studies that provided risk estimates for former users compared with current users, and none that provided risk estimates by time since quitting smokeless tobacco use. Detailed information on the six identified observational studies is presented in Table 2.21 and Table 2.22.

Two cohort studies, one in Sweden (Luo et al., 2007) and one in Norway (Boffetta et al., 2005), examined the association between oral snuff use and risk of oral cancer. Data on snuff use were collected using questionnaires, and cancer outcome data were obtained through linkage to cancer registries. The follow-up period between exposure and outcome was 12–35 years. Both analyses accounted for potential confounding due to smoking. Neither study found an association between snuff use (former or current) and risk of oral cancer; they reported risk estimates for former users of 0.7 (95% CI, 0.1–5.0) (Luo et al., 2007) and 1.0 (95% CI, 0.3–3.5) (Boffetta et al., 2005). [The Working Group noted the small number of incident oral cancers in former snuff users in both studies: 1 event in the study in Sweden (Luo et al., 2007) and 3 events in the study in Norway (Boffetta et al., 2005). The Working Group noted the absence of repeat assessment of status of snuff use as an important limitation in these studies, particularly given the long follow-up period. In addition, neither of the studies adjusted for alcohol consumption.]

Four case–control studies examined the risk of oral cancer in former users of smokeless tobacco. Of these, three were conducted in Sweden (Lewin et al., 1998; Schildt et al., 1998; Rosenquist, 2005) and examined oral snuff use. Exposure data were collected using questionnaires, and cancer outcome data were obtained through linkage to hospital or cancer registries. Controls from population-based registries were matched to cases. All three studies accounted for potential confounding due to smoking either by statistical adjustment or by providing stratified estimates in never-smokers. Two studies found 1.5–1.8-fold non-statistically significant increased risk of oral cancer in former oral snuff users compared with never-users, whereas no association was observed in current users (OR, 0.7 and 1.0). In the third study (Rosenquist, 2005), using never-users as the reference group, former users had a lower risk of oral cancer (OR, 0.3; 95% CI, 0.1–0.9) compared with current users (OR, 1.1; 95% CI, 0.5–2.5). [All three studies were conducted in Sweden, where reported associations between current snuff use and risk of oral cancer are weak. A role for reverse causation in the observed elevated estimates cannot be ruled out.]

The fourth case–control study, conducted in Yemen, found a significantly elevated risk of oral

Table 2.21 Cessation of smokeless tobacco use and risk of oral cancer – cohort studies

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure categories (number of cases)	Number of cases	RR (95% CI)	Comments
Luo et al. (2007) Sweden	Cohort study of 279 897 male construction workers in the Swedish building industry in 1978–1992 Detailed information on smoking and snus use collected through personal interview Oral cancer incidence data collected thorough complete linkage to population and health registries 12-yr follow-up (until 2004)	Oral cancer (ICD-7 codes 140, 141, 143, and 144 not including cancers of the salivary glands, pharynx, or larynx)	Snus use: Never-users of any tobacco Former users Current users	 50 1 9	 1.0 (ref) 0.7 (0.1–5.0) 0.9 (0.4–1.8)	Association between snus use and oral cancer was adjusted for age and BMI Former snus user was defined on entry into study; changes in habit were not accounted for Very small number of exposed cases
Boffetta et al. (2005) Norway	Cohort study in Norwegian general population that included a probability sample of the general adult population from the 1960 census who were alive on 1 January 1966 Questionnaires were mailed for collection of data on smokeless tobacco use 35-yr follow-up completed through cancer registry linkage until 2001 Study included only men (n = 10 136)	Oral and pharyngeal cancer (ICD-7 codes 141–148)	Snus use: Never-users Former users Current users	 25 3 6	 1.00 (ref) 1.04 (0.31–3.50) 1.13 (0.45–2.83)	Adjusted for age and smoking Former users were defined at entry into study, with no repeat assessment No clear definition of former users

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; N/A, not available; ref, reference; RR, relative risk; yr, year or years.

Table 2.22 Cessation of smokeless tobacco use and risk of oral cancer – case–control studies

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of cases/ controls	OR (95% CI)	Comments
Lewin et al. (1998) Stockholm (Sweden)	Registry-based case–control study Included men registered in hospital-based or population-based registries in 2 geographical regions, aged 40–79 yr in 1988–1990 128 oral cancer cases, 756 randomly selected controls matched on age, sex, region, and vital status Exposure data collected through personal interview	Oral cancer	Oral moist snuff: Never-users Former users Current users Ever-users	 103/550 15/41 10/50 25/91	 1.0 (ref) 1.8 (0.9–3.7) 1.0 (0.5–2.2) 1.4 (0.8–2.4)	Estimates adjusted for age, region, smoking, and alcohol consumption
Schildt et al. (1998) Sweden	Population-based case–control study Oral cancer cases confirmed by histopathology and registered in 4 northern regions of Sweden in 1980–1989 Controls from population registries matched on age, sex, county, and vital status and year of death where applicable Questionnaires mailed to collect information on tobacco use (smoking and moist snuff)	Oral cancer (ICD-7 codes 140, 141, 143–145).	Oral moist snuff: Never-users Former users Current users In never-smokers: Never-users Former users Current users	 287/282 28/18 23/54 124/144 9/4 19/23	 1.0 (ref) 1.5 (0.8–2.9) 0.7 (0.4–1.1) 1.0 (ref) 1.8 (0.9–3.5) 0.7 (0.4–1.2)	Estimates adjusted for age, sex, and county of residence. Smoking was not adjusted for, but stratified estimates were provided A former smoker or former snuff user was defined as a person who had quit smoking or snuff use ≥ 1 yr before the diagnosis
Rosenquist (2005) Sweden	Hospital-based case–control study in Sweden in 2000–2004 132 oral cancer cases (91 men) identified from 2 hospitals reflecting 80% participation rate of cases in the region. 320 controls (215 men) matched on age, sex, and county from the population registry. Data were collected by interview; oral examination and HPV testing were completed	Oral cancer	Oral snuff: Never-users Former users Current users	 112/255 7/34 13/31	 1.0 (ref) 0.3 (0.1–0.9) 1.1 (0.5–2.5)	ORs adjusted for smoking and total alcohol consumption. Further adjustment for HPV status had minor effects A former snuff user was defined as a person who had quit the habit ≥ 6 months before the interview

Table 2.22 (continued)

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of cases/ controls	OR (95% CI)	Comments
Nasher et al. (2014) Yemen	Hospital-based case–control study. Cases were confirmed by histopathology Oral cancer cases and age- and sex-matched controls	Oral cancer in users of *shammah* dipping	*Shammah*: Never-users Former users Current users	 11/98 7/8 42/14	 1.0 (ref) 12.6 (3.3–48.2) 39 (14–105)	Estimates were adjusted for age, sex, EBV status, and tobacco smoking

CI, confidence interval; EBV, Epstein–Barr virus; HPV, human papillomavirus; ICD, International Classification of Diseases; ref, reference; RR, relative risk; yr, year or years.

cancer in former *shammah* users compared with non-users (OR, 12.6; 95% CI, 3.3–48.2), which was significantly lower than that in current users (OR, 39; 95% CI, 14–105) (Nasher et al., 2014). [The Working Group noted that the estimates were based on a small number of former chewers; no definition was provided with respect to duration of cessation, and the estimates were not adjusted for alcohol consumption.]

(b) Risk of OPMDs

Four cohort studies, two case–control studies, and two cross-sectional studies have examined the association between former use of smokeless tobacco and risk of OPMDs. [Most of these studies were well powered with sufficient sample size to estimate overall effects, but they tended to have small numbers of former users.] Many of these studies reported risk estimates using never-users as the reference group, and some studies reported only the prevalence of lesions across exposed groups (Table 2.23).

The four cohort studies were all conducted in the USA: two were in baseball players, and two were large population-based cohorts. Three of the four studies diagnosed leukoplakia as the outcome of interest at baseline entry into the study, whereas Shulman et al. (2004) diagnosed oral mucosal lesions. Histopathological confirmation was indicated in only one study (Ernster et al., 1990). All four studies examined use of oral snuff and chewing tobacco; Sinusas et al. (1992) also examined use of moist snuff. In these studies, former users were categorized at study entry as past users, with no further definition with regard to duration of cessation, except in the study of Ernster et al. (1990), in which former users were defined as past users who had used smokeless tobacco more than once per month in the past and who had quit use ≥ 1 month ago. Three studies found no increased risk in former users of smokeless tobacco compared with never-users and found increased risk estimates for current users (Ernster et al., 1990; Tomar et al., 1997; Shulman et al., 2004). Sinusas et al. (1992) found a prevalence of leukoplakia in former users equivalent to that in never-users (6%). Current users had a much higher prevalence of lesions (37%), corresponding to a > 9-fold increase compared with former smokeless tobacco users and non-users (Sinusas et al., 1992). [In two studies (Ernster et al., 1990; Sinusas et al., 1992), chewing tobacco use and snuff use were combined to generate risk estimates; it is likely that snuff and chewing tobacco may reflect differential risks towards oral cancer. In the other two studies (Tomar et al., 1997; Shulman et al., 2004), multiple OPMDs were grouped together; because some of these may not be etiologically related to smokeless tobacco use, these results should be interpreted with caution.]

Two case–control studies were identified, one in the USA and one in Uzbekistan. In the study in Uzbekistan, risk estimates for former users of *naswar* (*nass*) were slightly lower than those for current users when compared with never-users (Evstifeeva and Zaridze, 1992). The study in the USA (Fisher et al., 2005) reported risks of leukoplakia for smokeless tobacco use and snuff use separately. For both products, higher risk estimates were found for current users than for former users compared with never-users. [Both studies accounted for smoking and other potential confounding factors, but neither of the studies defined former use with respect to the duration of cessation. In addition, the criteria for identification of leukoplakia and pre-leukoplakia were not defined in the study in Uzbekistan.]

One cross-sectional study, conducted in Uzbekistan, reported percentages of leukoplakia and pre-leukoplakia that were similar for former and current *naswar* use: 11.5% for former use and 12% for current use, compared with 2.2% in never-users (Zaridze et al., 1986). [No definition was provided for former users.] The other cross-sectional study, conducted in Yemen, included 346 people diagnosed with leukoplakia-like lesions based on the Axell criteria. Khat

Table 2.23 Cessation of smokeless tobacco use and risk of OPMDs

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of participants/ cases/controls (% with OPMDs)	RR (95% CI)	Comments
Cohort studies						
Ernster et al. (1990) USA	Cohort of 1109 baseball players who underwent training in 1988 (median age, 18 yr), of whom 75% used snuff and 21% chewed tobacco Leukoplakia was identified by dentists on entry and was biopsy-confirmed	Leukoplakia (as per the Greer and Poulson criteria)	Smokeless tobacco: Never-users Former users Current chewing tobacco users Current snuff users	 493 (1.4%) 138 (1.4%) 88(17.2%) 304 (55.6%)	 1.0 (ref) 1.0 (0.2–5.0) 14.5 (5.7–36.7) 86.9 (39.9–189.5)	Analysis adjusted for age, race, smoking, alcohol consumption, and dental hygiene Smokeless tobacco use defined at entry Snuff users had a significantly increased prevalence of leukoplakia compared with chewing tobacco users, OR: 4.4 (2.4–9.3) Former users were those who had used smokeless tobacco more than once a month in the past but had not used it within the previous month
Sinusas et al. (1992) Florida (USA)	Cohort of 206 professionals in baseball organization, of whom 42.7% were current users and 16.5% were former users of smokeless tobacco (moist snuff and chewing tobacco)	Leukoplakia (Greer and Poulson and Axell criteria)	Moist snuff and chewing tobacco: Non-users Former users Current seasonal users Current year-round users	[Crude estimates based on reported numbers] 79 (6.0%) 32 (5.9%) 24 (7.6%) 39 (37.1%)	 1.0 (ref) [0.99 (0.18–5.35)] [1.32 (0.24–7.22)] [9.32 (3.29–26.37)]	No definition was given for former users No adjustment was made for smoking, but only 7 of the 206 participants were smokers (3.4%); 4 also used smokeless tobacco
Tomar et al. (1997) USA	Cohort of 17 206 children aged 12–17 yr who participated in the 1986–1987 National Survey of Oral Health in schoolchildren in the USA, of whom 3.1% used any smokeless tobacco, 2.0% used any snuff, and 1.5% used any chewing tobacco	Oral mucosal lesions classified using Greer and Poulson and Axell criteria as "white or whitish oral soft-tissue lesions"	Chewing tobacco: Never-users Former users Current users Snuff: Never-users Former users Current users	 5195 (3.0%) 527 (6.0%) 273 (19.6%) 5359 (1.9%) 329 (5.6%) 307 (34.9%)	 1.0 (ref) 1.3 (0.7–2.2) 2.5 (1.3–5.0) 1.0 (ref) 2.4 (1.0–6.1) 18.4 (8.5–39.8)	RRs adjusted for age, smoking, and alcohol consumption Former users of snuff or chewing tobacco were defined as those who reported that they had ever used these products but were not using them at the time of the survey

Table 2.23 (continued)

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of participants/ cases/controls (% with OPMDs)	RR (95% CI)	Comments
Shulman et al. (2004) USA	A sample of 17 235 people aged ≥ 17 yr from the Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III) who underwent oral examination by dentists for identification of oral lesions Lifestyle data were collected by interview	48 different oral mucosal lesion types classified based on the WHO *Guide to epidemiology and diagnosis of oral mucosal diseases and conditions*	Smokeless tobacco: Never-users Former users Current users	 8143 (23.8%) 183 (12.8%) 371 (60.3%)	 1.00 (ref) 0.53 (0.25–1.13) 3.90 (2.75–5.55)	Analyses adjusted for age, sex, denture status, race, and smoking Specific type of smokeless tobacco used was not indicated Definition of former users is unclear Oral lesions considered included denture-related (8.4%) and tobacco-related lesions (smokeless tobacco-related and nicotine stomatitis) (4.7%)
Cross-sectional studies						
Zaridze et al. (1986) Uzbekistan	Cross-sectional study in Uzbekistan 1569 people from a population-based cohort of men invited for medical examination by local authority; 42% used *nass* Oral lesions clinically diagnosed, and exposure assessed by interview	Leukoplakia and pre-leukoplakia	*Nass*: Never-users Former users Current users	 625 (2.2%) 26 (11.5%) 525 (12%)	 1.0 (ref) NR 5.6 (3.4–9.5)	Estimates are provided for never-smokers It is unclear whether these estimates were adjusted for potential confounding factors Definition of former users is unclear
Al-Tayar et al. (2015) Yemen	Cross-sectional study in 2014 in Dawan Valley, Yemen, involving 346 male residents aged ≥ 18 yr. An interview-based questionnaire was used to collect demographic, oral hygiene, and *shammah* use information Smokers and khat users were excluded	Leukoplakia-like lesions (Axell criteria) 80 leukoplakias were diagnosed at grade 1–4 and 266 at grade 0	*Shammah*: Never-users Former users Current users	 248 (NR) 30 (NR) 68 (NR)	 1.00 (ref) 3.65 (1.40–9.50) 12.99 (6.34–26.59)	Analyses were adjusted for age, education level, and frequency of *shammah* use Former *shammah* users were those individuals who had previously consumed *shammah* but stopped their consumption for ≥ 1 yr

Table 2.23 (continued)

Reference Location	Study population, number of participants, study period, follow-up period	Outcome assessed	Exposure category	Number of participants/ cases/controls (% with OPMDs)	RR (95% CI)	Comments
Case–control studies						
Evstifeeva and Zaridze (1992) Uzbekistan	Case–control study in a region of Uzbekistan with high incidence of oral and oesophageal cancer 191 men with leukoplakia and 466 controls Data on use of *nass* quid, cigarette smoking, and alcohol consumption were collected by interview from 1569 men	Leukoplakia and pre-leukoplakia	*Nass*: Never-users Former users Current users	 66/282 7/13 118/171	 1.00 (ref) 3.00 (1.08–8.32) 3.86 (2.60–5.72)	Analyses adjusted for age, smoking, and alcohol consumption
Fisher et al. (2005) West Virginia (USA)	Hospital-based case–control study in the USA 90 cases (54 men) aged ≥ 18 yr with leukoplakia with histopathological confirmation of hyperkeratosis were compared with 78 (37 men) controls with periapical cysts from the same surgical pathology unit Smokeless tobacco and related data collected by postal questionnaires	Leukoplakia (ICD-9 classification)	Smokeless tobacco: Never-users Former users Current users Snuff: Never-users Former users Current users	 55/64 19/9 16/5 64/71 8/5 15/2	 1.00 (ref) 2.73 (0.69–10.84) 9.21 (1.49–57.00) 1.00 (ref) 0.98 (0.17–5.61) 30.08 (2.67–338.48)	ORs adjusted for age, sex, smoking, alcohol consumption, and denture status

CI, confidence interval; ICD, International Classification of Diseases; NHANES, National Health and Nutrition Examination Survey; NR, not reported; OPMDs, oral potentially malignant disorders; OR, odds ratio; ref, reference; RR, relative risk; WHO, World Health Organization.

users and smokers were excluded. Past history of *shammah* use was reported to increase the risk of oral cancer by > 3-fold (3.65; 95% CI, 1.40–9.50). Current *shammah* use further increased the risk of oral cancer in this population (Al-Tayar et al., 2015). [The study appears to be of limited power because of a small number of former users. Also, duration of cessation was not defined.]

Although the body of evidence appeared inconsistent with regard to the direction and the magnitude of risk of OPMDs, the RR estimates for former users of smokeless tobacco were generally lower than those for current users when compared with never-users as the reference group within each study. To clarify whether the distribution of covariance within individual studies could explain or potentially reveal underlying risk trends, the Working Group undertook additional analysis (Table 2.24). First, the RR in former users compared with current users was estimated for each study based on the Dirichlet–multinomial distribution method (Gelman et al., 1995). Next, the recalculated risk estimates and 95% CIs were used to derive the variance and covariance matrices of case and control populations based on the tri-gamma distribution of the corresponding variables, which were then approximated. [The meta-estimate reflected nearly 70% reduction in RR for former users compared with current users of smokeless tobacco (OR, 0.30; 95% CI, 0.14–0.46).]

2.3.4 Chewing areca nut products (including betel quid) with added tobacco

Two prospective cohort studies (Jayalekshmi et al., 2009, 2011), one nested case–control study (Muwonge et al., 2008), two case–control studies (Balaram et al., 2002; Znaor et al., 2003), and a recent meta-analysis (Gupta et al., 2022) assessed the effect of cessation of chewing areca nut with added tobacco on the incidence of oral cancer (Table 2.25). To complement the evidence available from the published literature, the Working Group undertook primary data analyses from unpublished data from one cohort study and one case–control study, both conducted in India and providing information on incidence of oral cancer in relation to time since chewing cessation (Table 2.26).

One intervention study and three follow-up studies focusing on assessing the relationship between cessation of chewing areca nut with added tobacco and the incidence of leukoplakia and OSF at the 5-year and 10-year follow-ups (Gupta et al., 1986; Murti et al., 1990; Gupta et al., 1992, 1995) were available to the Working Group (Table 2.27). Two additional case–control studies focused on the incidence of OPMDs as the outcome (Amarasinghe et al., 2010a; Worakhajit et al., 2021) (Table 2.28).

(a) Studies of oral cancer

(i) Evidence from the published literature

See Table 2.25.

The two reports of Jayalekshmi et al. (2009, 2011) were based on a large cohort established as a part of the cancer registry in Karunagappally in Kerala, India. The cohort included 66 277 men and 78 140 women; by 2005, 160 cases of oral cancer in men and 92 in women were identified from the cancer registry. The association between chewing areca nut with added tobacco and risk of oral cancer was examined overall for both men and women, as well as in men who were never and current bidi smokers. In men, the risk of oral cancer in former chewers (OR, 2.1; 95% CI, 1.3–3.6) was comparable to that in current chewers (OR, 2.4; 95% CI, 1.7–3.3). Among never bidi smokers, the RR estimate in former chewers (OR, 3.2; 95% CI, 1.1–9.6) was lower than that in current chewers (OR, 5.4; 95% CI, 3.0–9.0); in current bidi smokers, the risk estimate for former chewers was not significantly elevated compared with never-chewers (OR, 1.3; 95% CI, 0.6–2.9). In women, a 9-fold increased risk of oral cancer was reported in former chewers (OR, 9.2; 95% CI,

Table 2.24 Cessation of smokeless tobacco use and risk of OPMDs – recalculation of the relative risk for former chewers versus current chewers, and meta-analysis of results

Reference	Study design	Effect size for chewing habit (versus never-chewers)		Effect size for chewing habit with consideration of covariance
		Former chewers Estimate (95% CI)	Current chewers Estimate (95% CI)	Former chewers versus current chewers Estimate (95% CI)
Ernster et al. (1990)	Cohort	1.0 (0.2–5.0)	14.5 (5.7–36.7)	0.07 (0.01–0.44)
Sinusas et al. (1992)	Cohort	0.99 (0.18–5.35)	9.32 (3.29–26.37)	0.11 (0.02–0.48)
Tomar et al. (1997)	Cohort	1.3 (0.7–2.2)	2.5 (1.3–5.0)	0.52 (0.31–0.87)
Shulman et al. (2004)	Cohort	0.5 (0.3–1.1)	3.9 (2.8–5.6)	0.14 (0.06–0.30)
Al-Tayar et al. (2015)	Cross-sectional	3.7 (1.4–9.5)	13.0 (6.3–26.6)	0.28 (0.11–0.73)
Evstifeeva and Zaridze (1992)	Case–control	3.0 (1.1–8.3)	3.9 (2.6–5.5)	0.77 (0.28–2.14)
Fisher et al. (2005)	Case–control	2.7 (0.7–10.8)	9.2 (1.5–57.0)	0.30 (0.05–1.69)
Results of meta-analysis				
Random-effect model				0.30 (0.14–0.46)
Fixed-effect model				0.34 (0.22–0.45)

CI, confidence interval; OPMDs, oral potentially malignant disorders.

4.6–18.1), whereas a nearly 5-fold increased risk was reported in current chewers (OR, 5.5; 95% CI, 3.3–9.0) compared with never-chewers. This study also examined risk of oral cancer by time since quitting chewing areca nut with added tobacco. In men, ≥ 10 years of quitting appeared to reduce risks to levels comparable to those in never-chewers, with differences in estimates that were not statistically significant. No such reduction was noted in women (Jayalekshmi et al., 2009, 2011). [The higher risk in former chewers compared with current chewers in women is difficult to understand and cannot be attributed to reverse causation, because the risk of oral cancer in those with ≥ 10 years of quitting was still higher than that in current chewers. Estimates were not adjusted for tobacco smoking and alcohol consumption, although these behaviours were reported to be rare in women in this population.]

Muwonge et al. (2008) enrolled 282 incident oral cancer cases and 1410 matched controls in a case–control study nested in the cohort of a randomized controlled study in Trivandrum, India (Sankaranarayanan et al., 2000). In this study, the RR of chewing areca nut with added tobacco for the incidence of oral cancer was 4.3 (95% CI, 3.1–6.1) in current chewers and 11.9 (95% CI, 7.0–20.4) in former chewers compared with never-chewers. [The Working Group noted that the higher risk reported for former chewers could result from reverse causation.]

A matched case–control study enrolled 591 cases of oral cancer and 582 controls who were frequency-matched (on age, sex, and centre) in three centres in Bangalore, Madras, and Trivandrum in southern India (Balaram et al., 2002). In men, the risk of oral cancer in former chewers decreased progressively with increasing time since chewing cessation compared with current chewers, reaching a reduction of 25% (RR, 0.75; 95% CI, 0.23–2.52) ≥ 10 years after cessation. In women, on contrast, the risk of oral cancer was higher for ≥ 10 years of cessation than

Table 2.25 Cessation of chewing of areca nut products (including betel quid) with added tobacco and risk of oral cancer – observational studies

Reference Location	Study population, sample selection, response rate	Study design, number of participants, study period, follow-up time	Exposure category Number of exposed cases/controls	RR (95% CI)	Comments
Cohort studies					
Jayalekshmi et al. (2009) India	Women aged 30–84 yr in Karunagappally, Kerala, were enrolled with house-to-house surveys to have baseline information The response rate was 93%	Prospective cohort study designed to link 78 140 enrolled women participating in the baseline survey with the cancer registry. Baseline information was collected on lifestyle, including tobacco chewing, and sociodemographic factors in 1990–1997. By the end of 2005, 92 oral cancer cases were identified	Women: Never-chewers: 25 Former chewers: 14 Current chewers: 53 Duration of cessation (yr): Current chewers: 53 < 10: 7 ≥ 10: 4 Never-chewers: 25	 1.0 (ref) 9.2 (4.6–18.1) 5.5 (3.3–9.0) 1.0 (ref) 1.7 (0.8–3.7) 2.6 (0.9–7.2) 0.2 (0.1–0.3)	Poisson regression model was used to calculate relevant estimates Adjusted for age and family income Estimates not adjusted for tobacco smoking and alcohol consumption; however, according to the authors these habits are rare in women in this population
Jayalekshmi et al. (2011) India	Men aged 30–84 yr in Karunagappally, Kerala, were enrolled with house-to-house surveys to have baseline information The response rate was 93%	The same prospective cohort study was designed as above, but the target participants were 66 277 men. By the end of 2005, 160 oral cancer cases were identified	Men (cases/person-yr): Overall: Never-chewers: 64 Former chewers: 19 Current chewers: 75 In never bidi smokers: Never-chewers: 18 Former chewers: 4 Current chewers: 37 In current bidi smokers: Never-chewers: 38 Former chewers: 7 Current chewers: 27 Duration of cessation (yr): Current chewers: 75 < 10: 12 ≥ 10: 2 Never-chewers: 64	 1.0 (ref) 2.1 (1.3–3.6) 2.4 (1.7–3.3) 1.0 (ref) 3.2 (1.1–9.6) 5.4 (3.0–9.0) 1.0 (ref) 1.3 (0.6–2.9) 1.3 (0.8–2.1) 1.0 (ref) 1.1 (0.6–2.0) 0.3 (0.1–1.2) 0.4 (0.3–0.6)	Poisson regression model was used to calculate relevant estimates Adjusted for age and family income. Estimates not adjusted for alcohol consumption

Table 2.25 (continued)

Reference Location	Study population, sample selection, response rate	Study design, number of participants, study period, follow-up time	Exposure category Number of exposed cases/controls	RR (95% CI)	Comments
Case–control studies					
Balaram et al. (2002) India	Patients with incident oral cancer and their hospital-based matched controls in Bangalore, Madras, and Trivandrum centres	Matched case–control study conducted in 1996–1999 Case group: 591 incident cases of oral cancer Control group: 582 hospital controls, frequency-matched to cases on age and sex and on centre (relatives and friends of patients admitted to hospitals because of diseases other than oral cancer in Bangalore and Madras, and outpatients in Trivandrum) Confounding factors adjusted for in the logistic regression model were age, location, education level, and only for men: tobacco smoking (never/ever) and alcohol consumption (never/ever)	Men: Duration of cessation (yr): Current chewers: 120/37 < 10: 45/14 ≥ 10: 14/6 Women: Duration of cessation (yr): Current chewers: 203/29 < 10: 31/6 ≥ 10: 17/3	 1.0 (ref) 1.02 (0.45–2.29) 0.75 (0.23–2.52) 1.0 (ref) 0.72 (0.23–2.21) 0.97 (0.23–4.11)	The sex-related differences in the results may be attributed to selection bias for women, who may be less likely to go to hospitals, because the proportion of ever-chewers in women in such hospital-based controls was lower than that in women in the general population
Znaor et al. (2003) India	Male patients with oral cancer as cases in Chennai (Tamil Nadu) and Trivandrum (Kerala)	Case–control study conducted in 1993–1999 Case group: 1563 oral cancer cases Control group: 1711 male patient controls from both centres and 1927 male healthy hospital visitors in Chennai Confounding factors adjusted for in the logistic regression model were age, location, education level, tobacco smoking, and alcohol consumption (never/ever)	Duration of cessation (yr): Current chewers: 640/460 2–4: 93/41 5–9: 59/20 10–14: 30/19 ≥ 15: 30/19	 1.0 (ref) 1.15 (0.75–1.77) 1.60 (0.92–2.81) 0.71 (0.37–1.35) 0.67 (0.36–1.26)	

Table 2.25 (continued)

Reference Location	Study population, sample selection, response rate	Study design, number of participants, study period, follow-up time	Exposure category Number of exposed cases/controls	RR (95% CI)	Comments
Muwonge et al. (2008) India	People aged ≥ 35 yr in Trivandrum District	Nested case–control design based on data from a randomized control trial for oral cancer screening conducted in 1996–2004 in Trivandrum (Kerala) Case group: 282 incident oral cancer cases Control group: 1410 controls matched on sex, age (± 1 yr), area of residence, and screening participation	Overall: Never-chewers: 80/915 Current chewers: 160/445 Former chewers: 42/50 Men: Never-chewers: 64/561 Current chewers: 78/222 Former chewers: 21/32 Women: Never-chewers: 16/354 Current chewers: 82/223 Former chewers: 21/18	 1.0 (ref) 4.3 (3.1–6.1) 11.9 (7.0–20.4) 1.0 (ref) 2.7 (1.8–4.2) 5.9 (3.0–11.7) 1.0 (ref) 9.5 (5.0–18.0) 39.0 (15.0–101.8)	The high risk in former chewers compared with current chewers was observed in both sexes in this study. It may be the result of reverse causation (i.e. the more severe cases are more likely to quit chewing)
Meta-analysis					
Gupta et al. (2022)	2 cohort and 4 case–control studies and one case–control study nested in a randomized trial		Never-chewers Former chewers Current chewers Duration of cessation (yr): < 10 > 10	1.0 (ref) 6.87 (4.10–11.52) 6.29 (3.83–10.33) 1.21 (0.90–1.63) 0.72 (0.48–1.07)	6 of the 7 studies were restricted to men or provided sex-specific results; 4 studies did not provide a clear definition of former users; 2 case–control studies provided relative risks of oral cancer by duration of cessation

CI, confidence interval; ref, reference; RR, relative risk; yr, year or years.

for < 10 years of cessation. [A selection bias may explain the results in women – who may be less likely to go to hospitals – because the proportion of ever-chewers in women in such hospital-based controls was lower than that in women in the general population.]

Another case–control study, conducted in 1993–1999 at the cancer institute in Chennai (Tamil Nadu) and the Regional Cancer Centre in Trivandrum (Kerala), India, enrolled 1563 male oral cancer cases and 3638 male hospital controls (Znaor et al., 2003). The risk estimate of oral cancer compared with current chewers decreased by 29% (RR, 0.71; 95% CI, 0.37–1.35) for 10–14 years of cessation and by 33% (RR, 0.67; 95% CI, 0.36–1.26) for ≥ 15 years of cessation. [The selection of the control group was different: the hospital control from both centres and an additional healthy control from only one of the two centres. In addition, compared with cases of oral cancer, the control group was younger and educated. Although these demographic characteristics were considered in the multivariate analysis, residual confounding may still exist.]

In the last days of the Working Group meeting, a meta-analysis was made available to the Working Group that combined seven reports to assess the potential benefit of long-term cessation of chewing areca nut with added tobacco (Gupta et al., 2022). [The meta-analysis includes all the cohort and case–control studies reported above (Balaram et al., 2002; Znaor et al., 2003; Muwonge et al., 2008; Jayalekshmi et al., 2009, 2011).] The meta-RR of oral cancer for former chewers with < 10 years of cessation compared with current chewers was increased (1.21; 95% CI, 0.90–1.63) and for former chewers with > 10 years of cessation was decreased (0.72; 95% CI, 0.48–1.07). [The increased risk after < 10 years of cessation could be due to reverse causation. The sample size was still insufficient to reach statistical significance in the reversal of risk of oral cancer after long-term cessation.]

(ii) Evidence from primary data analyses

See Table 2.26.

Data collected at two sites in India were used for primary analysis by the Working Group to assess the impact of quitting chewing betel quid with added tobacco on the risk of oral cancer.

The first primary analysis used data derived from the cluster-randomized controlled trial in Trivandrum, India (Sankaranarayanan et al., 2000). The data were from a cohort of 191 870 participants aged ≥ 35 years enrolled in 1996–2006. Incident oral cancer was ascertained until 31 December 2009; the average follow-up period was 7 years. The main exposure of interest included the chewing status (current, former, and never) and duration of cessation. The major confounders were adjusted for in the Cox proportional hazards regression model. Per year of quitting chewing betel quid with added tobacco, the risk of oral cancer decreased significantly (HR, 0.97; 95%, 0.96–0.99). However, for participants with > 15 years of cessation, the risk of oral cancer remained high (HR, 2.5; 95% CI, 1.6–3.7) compared with current chewers. Compared with people with < 2 years of cessation, those with > 10 years of cessation had a lower risk of oral cancer (HR for 10–15 years, 0.8; 95% CI, 0.3–2.0; HR for > 15 years, 0.7; 95% CI, 0.4–1.4), although this was not statistically significant. [Duration of cessation was imputed using current age and duration of chewing, which may explain the wide 95% CIs. There are issues with identifiability and collinearity of time since quitting with duration and age. The median age was different between current and former chewers: 52 years for current chewers and 62–65 years for the several categories of former chewers.]

The second primary analysis used data derived from cancer hospitals in India. A case–control study design was applied. Cases were patients with oral cavity cancer diagnosed in the cancer hospital from three cities: Mumbai, Varanasi, and Guwahati. Controls

Table 2.26 Cessation of chewing of areca nut products (including betel quid) with added tobacco and risk of oral cancer – primary data analyses performed by the Working Group

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/controls	OR (95% CI)	Comments
Kerala oral cancer screening trial (several previous publications)	Kerala, India	Cluster-randomized trial of 191 870 participants aged ≥ 35 yr who were recruited in 1996–2006 and followed up until 31 December 2009. Data on exposures collected at baseline was used for analysis The analysis was Cox proportional hazards regression The key exposure was duration of cessation of chewing of betel quid (primarily with added tobacco). This metric was derived using simple, single-value imputation of age at initiation of chewing (10-year birth cohort and sex-specific, estimated from GATS India 2009–2010), duration of chewing, and age at study participation. Individuals with negative duration of cessation were excluded from analyses Analyses were adjusted for age, sex, education level, chewing duration and intensity, smoking duration and intensity, and alcohol consumption duration and intensity (days per week of alcohol consumption) Two sets of analyses were conducted: (1) analyses restricted to ever-chewers (n = 40 860), and (2) analyses restricted to former chewers (n = 3441)	Oral cancer incidence during 7 yr of follow-up	202 cases in ever-chewers, 65 cases in former chewers		Difference between categories of duration of cessation was not statistically significant Duration of cessation was imputed using current age and duration of chewing. There are issues with identifiability and collinearity of duration of cessation with duration of use and age There is age confounding between current and former chewers (the median age is 52 yr for current chewers, and 62, 62, 62, 59, and 65 yr for former chewers with < 2, 2–5, 5–10, 10–15, and > 15 yr of cessation, respectively)
					Compared with current chewers:	
				Current chewers:		
				202/37 419	1.0 (ref)	
				Duration of cessation (yr):		
				< 2: 13/567	3.7 (2.1–6.5)	
				2–5: 6/195	5.1 (2.2–11.8)	
				5–10: 12/390	5.1 (2.8–9.4)	
				10–15: 7/435	3.1 (1.4–6.5)	
				> 15: 27/1854	2.5 (1.6–3.7)	
					Compared with quitting < 2 yr:	
				Duration of cessation (yr):		
				< 2	1.0 (ref)	
				2–5	1.4 (0.5–3.8)	
				5–10	1.4 (0.6–3.1)	
				10–15	0.8 (0.3–2.0)	
				> 15 yr	0.7 (0.4–1.4)	
				Per year of cessation	0.97 (0.96–0.99)	

Table 2.26 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/controls	OR (95% CI)	Comments
Unpublished, Tata Memorial Centre, Mumbai. Study is part of a GWAS of buccal cancers	Mumbai, Varanasi, and Guwahati, India	Hospital-based case–control study of patients with buccal mucosa cancer and controls, matched on 5-year age, sex, and site The main exposure was duration of cessation of chewing Logistic regression analyses were adjusted for age, sex, study site, alcohol consumption intensity, smoking duration and intensity, and chewing duration and intensity	Buccal mucosa cancers	391 cancers in current chewers, 99 cancers in former chewers, 1367 controls		Inverse relationship between the categories of duration of cessation and the risk of buccal mucosa cancer
					Compared with current chewers:	
				Current chewers:		
				391/969	1.0 (ref)	
				Duration of cessation (yr):		
				< 1: 15/146	3.1 (1.4–7.1)	
				2–5: 25/136	1.5 (0.8–2.8)	
				5–10: 14/41	1.1 (0.4–2.5)	
				≥ 10: 45/75	0.7 (0.3–1.5)	
				Per year of cessation	0.98 (0.95–1.02)	

CI, confidence interval; GATS, Global Adult Tobacco Survey; GWAS, genome-wide association study; OR, odds ratio; ref, reference; yr, year or years.

matched on age (5-year band), sex, and site were selected from the hospital. The main exposures of interest were the status of chewing betel quid with added tobacco and duration of cessation. The confounding factors were adjusted for in the logistic regression analysis. There were 391 cancers in current chewers, 99 cancers in former chewers, and 1367 matched controls. A 2% reduction in risk of oral cavity cancer was calculated per year of cessation (OR, 0.98; 95% CI, 0.95–1.02). The risk of oral cavity cancer was lower in former chewers with > 10 years of cessation (OR, 0.7; 95% CI, 0.3–1.5) compared with current chewers. [Neither estimate was statistically significant.]

(b) Studies of OPMDs

(i) Intervention study

See Table 2.27.

The intervention study (Gupta et al., 1986) enrolled tobacco chewers and smokers older than 15 years in three districts in India in 1966: Ernakulam District in Kerala, Srikakulam District in Andhra Pradesh, and Bhavnagar District in Gujarat. This is currently the only study worldwide that was designed to evaluate the effectiveness of an education programme for tobacco users in reducing incidence of OPMDs. The intervention arm received primary prevention in the form of an education programme with professional advice provided by dentists and trained social scientists, as well as radio broadcasts and newspaper articles. Ernakulam District was the only one of the three districts in which chewing betel quid with added tobacco was the main habit in the population; therefore, only results from that district were relevant here. After the 5-year follow-up, the proportion of individuals who had stopped chewing betel quid with added tobacco was higher in the intervention cohort than in the control cohort (9% vs 3%), and the proportion of individuals who reduced the intensity of chewing betel quid with added tobacco was also higher in the intervention cohort than in the control cohort (28% vs 9%). The education programme showed significant effectiveness in reducing the risk of leukoplakia: reported rate ratios were 0.51 [95% CI, 0.28–0.93] in men and 0.19 [95% CI, 0.11–0.30] in women for chewers, and 0.20 [95% CI, 0.13–0.30] in men and 0.19 [95% CI, 0.02–2.12] in women for chewers who also smoked. [Because this study was not randomized, the effectiveness may be affected by unadjusted confounding factors, such as demographic characteristics. Age was not adjusted for, and only stratification by sex was provided. A second unadjusted confounding factor was baseline socioeconomic status, which may have differed between the intervention cohort and the control cohort (recruited 10 years earlier than the intervention cohort). Also, cases in the intervention cohort included individuals who had reduced the intensity of chewing, who had stopped chewing, and those who had continued chewing.]

Murti et al. (1990) reported on the cohorts in Ernakulam District, focusing on the incidence of OSF, with a follow-up period of 10 years. The education programme resulted in a RR reduction of OSF incidence of 62% (RR, 0.38; [95% CI, 0.06–2.24]) in men and 37% (RR, 0.63; [95% CI, 0.25–1.65]) in women for chewers. [The major limitation of this study is the small number of OSF events in chewers.]

Gupta et al. (1992) also reported on a 10-year follow-up of the cohorts, focusing on leukoplakia. The incidence of leukoplakia was reduced significantly, by 37% (RR, 0.63; [95% CI, 0.37–1.06]) in men and by 55% (RR, 0.45; [95% CI, [0.32–0.63]) in women for chewers, and by 63% (RR, 0.37; [95% CI, 0.25–0.54]) in men for chewers who also smoked. In a later report, Gupta et al. (1995) also reported on a 10-year follow-up by comparing the incidence of leukoplakia and of OLP between the "stopped" category (former chewers who stopped chewing ≥ 6 months ago) and "all others" (other categories combined) using the intervention

Table 2.27 Cessation of chewing of areca nut products (including betel quid) with added tobacco and risk of OPMDs – intervention study

Reference Location	Study population, sample selection, response rate	Study design, number of participants, intervention, study period, follow-up time	OPMD end-point	Exposure category Number of cases, intervention/ control	RR 95% CI)	Comments
Gupta et al. (1986, 1992, 1995); Murti et al. (1990) Kerala, India	Tobacco users (chewers and smokers) aged ≥ 15 yr in 3 districts in India Two distinct cohorts were selected in each district through house-to-house surveys to have an interview and a clinical mouth examination at baseline and regular follow-up ≥ 97% follow-up rate for the intervention cohort, and 84–95% follow-up rate for the control cohort	Prospective study with intervention cohort and control cohort Intervention cohort (n = 12 212) and control cohort (n = 6075) in Ernakulam District Recruitment in 1976–1985 for intervention cohort, and in 1966–1977 for control cohort 10-yr follow-up Intervention was an education programme through professional advice (dentist and social scientist) and social media Higher stoppage of chewing (15.1% vs 2.3% for men; 18.4% vs 7.8% for women) and of mixed chewing and smoking (3.8% vs 2.0% for men;13.2% vs 3.8% for women)	Incidence of leukoplakia	Chewing only: Men: [32/25] Women: [60/72] Mixed chewing and smoking: Men: [44/68] Women:	 0.63 [(0.37–1.06)] 0.45 [(0.32–0.63)] 0.37 [(0.25–0.54)] 0.52 [(0.01–29.85)]	10 yr of follow-up of the main study focusing on Ernakulam District in Kerala conducted by Gupta et al. (1986) Chewing betel quid with added tobacco was the main habit in the population in Ernakulam District in Kerala Results are crude incidence stratified by sex, not adjusted for age. Only 5-year age-adjusted incidence was reported for total tobacco use (rather than different categories) Baseline socioeconomic status may have differed between the intervention cohort and the control cohort (10 yr earlier than the intervention cohort)
	81–93% follow-up rate for the intervention cohort, and 71–75% follow-up rate for the control cohort	Intervention cohort (n = 6341 chewers) and control cohort (n = 3809 chewers)	Incidence of OSF	Men: 2/3 Women: 9/8	0.38 (0.06–2.24) 0.63 (0.25–1.65)	Murti et al. (1990). Analysis restricted to chewers only. Events of OSF are too rare to have sufficient statistical power

Table 2.27 (continued)

Reference Location	Study population, sample selection, response rate	Study design, number of participants, intervention, study period, follow-up time	OPMD end-point	Exposure category Number of cases, intervention/ control	RR 95% CI)	Comments
Gupta et al. (1986, 1992, 1995); Murti et al. (1990) (cont.)			Incidence of OLP	"stopped"/"all others":		Gupta et al. (1995). Part of the main study focusing on Ernakulam District in Kerala conducted by Gupta et al. (1986) with 10 yr of follow-up Only chewers in the intervention cohort were considered. The "stopped" category included former chewers who stopped chewing ≥ 6 months ago
				Men: 1/30	0.02 [(0.00–0.13)]	
				Women: 18/90	1.29 [(0.78–2.14)]	
			Incidence of leukoplakia	"stopped"/"all others":		
				Men: 4/33	0.81 [(0.29–2.28])]	
				Women: 5/52	0.30 [(0.12–0.75)]	

CI, confidence interval; OLP, oral lichen planus; OPMDs, oral potentially malignant disorders; OSF, oral submucous fibrosis; RR, relative risk; vs, versus.

cohort only. Cessation of chewing betel quid with added tobacco significantly reduced the incidence of leukoplakia, by 19% (RR, 0.81; 95% CI, 0.29–2.28) in men and 70% (RR, 0.30; 95% CI, 25–88%) in women for former chewers, whereas there was no effect of chewing cessation in reducing the incidence of OLP. [There was a lack of statistical power for OLP incidence because of too few OLP events.]

(ii) Observational studies

See Table 2.28.

In a case–control study in Sri Lanka, chewers of betel quid were categorized as daily, occasional, and former chewers (Amarasinghe et al., 2010a). Two thirds of the chewers used betel quid with added tobacco: 82% among the cases and 32% among the controls. The incidence of leukoplakia, OSF, and OLP were used as outcomes. For daily chewers, the risk of OPMDs increased 10-fold (OR, 10.6; 95% CI, 3.6–31.0) compared with never-chewers. For former chewers, the incidence of OPMDs increased 2-fold (OR, 2.4; 95% CI, 0.4–14.5), similarly to occasional chewers (OR, 2.0; 95% CI, 0.4–9.4). The Working Group calculated a lower, non-significant RR of OPMDs for former chewers compared with current chewers [OR, 0.23; 95% CI, 0.03–1.79]. [The Working Group noted two major limitations of this study: (i) the results were for a mixture of chewers of betel quid with and without tobacco, and (ii) no information on the time since quitting was available.]

A case–control study in northern Thailand (Worakhajit et al., 2021) was conducted in 2019–2021 to investigate the relationship between betel quid chewing and risk of OPMDs. This study enrolled 562 cases (people with identified OPMD) and 886 controls (people without OPMD). Using those with < 5 years of quitting as the reference group, those with ≥5 years of quitting had a slightly lower, but not statistically significantly so, RR of OPMDs (OR, 0.94; 95% CI, 0.22–3.92). [Not enough information on the number of cases by duration of quitting chewing was available to judge the strength of the results.]

2.3.5 Chewing areca nut products (including betel quid) without tobacco

Published evidence on the impact of quitting chewing areca nut products without tobacco on the risk of oral cancer consisted of four case–control studies with data in former chewers and current chewers compared with never-chewers (Table 2.29). In addition, a recent meta-analysis of 14 case–control studies provided estimates of oral cancer incidence after cessation of chewing areca nut without tobacco (Gupta et al., 2022). To complement the evidence available from the published literature, the Working Group undertook primary analyses from unpublished data from three large cohort studies and one case–control study providing information on incidence of oral cancer (Table 2.30) in relation to time since chewing cessation and age at quitting.

Published evidence on the impact of quitting chewing areca nut products without tobacco on the risk of OPMDs consisted of three case–control studies and two cross-sectional studies (Table 2.31). Similarly, the Working Group undertook primary analyses from unpublished data from three large cohort studies and one case–control study providing information on incidence of OPMDs in relation to time since chewing cessation and age at quitting (Table 2.32).

(a) Studies on oral cancer

(i) Evidence from the published literature

See Table 2.29.

Ko et al. (1995) reported on a hospital-based matched case–control study that assessed the independent effects of use of betel quid without tobacco, cigarette smoking, and alcohol consumption on oral cancer, as well as the synergistic effect of these behaviours. [Information on time since chewing cessation was lacking.] Current chewers were defined as those chewing ≥ 1 quid daily for

Table 2.28 Cessation of chewing of areca nut products (including betel quid) with added tobacco and risk of OPMDs – observational studies

Reference Location	Study population, sample selection, response rate	Study design, number of participants, study period, follow-up time	OPMDs end-point	Exposure category Cases/controls	OR (95% CI)	Interpretation/comments
Amarasinghe et al. (2010a) Sri Lanka	People aged ≥ 30 yr in Sabaragamuwa Province	Two-phase designed study Phase 1: Cross-sectional community survey with a house-to-house method to screen for OPMDs for 1029 people randomly selected by a multistage, stratified, clustered sampling technique Phase 2: Nested case–control study with a case group (n = 101) who were identified as having OPMDs (i.e. leukoplakia, erythroplakia, OSF, OLP) and a control group (n = 728) without OPMDs from Phase 1 Adjusted for sex, age, education level, occupation, BMI, tobacco smoking, and alcohol consumption	Leukoplakia, OSF, and OLP combined	Non-chewers: 4/277 Former chewers: 2/36 Occasional chewers: 3/83 Daily chewers: 92/332	Compared with non-chewers: 1.0 (ref) 2.4 (0.4–14.5) 2.0 (0.4–9.4) 10.6 (3.6–31.0)	Study based on a screening programme for OPMDs. Results were for a mixture of chewers with and without combined use of tobacco
Worakhajit et al. (2021) Thailand	People aged ≥ 40 yr in north-eastern Thailand	Case–control study design, conducted in 2019–2021 Community-based screening at the village level for 392 396 people with an oral cancer risk screening questionnaire administered by health-care volunteers 1448 people aged ≥ 40 yr were enrolled, including 562 with identified OPMD as the case group and 886 without OPMD as the control group	OPMDs	Duration of cessation (yr): < 5 ≥ 5	 1.00 (ref) 0.94 (0.22–3.92)	

BMI, body mass index; CI, confidence interval; OLP, oral lichen planus; OPMDs, oral potentially malignant disorders; OSF, oral submucous fibrosis; ref, reference; yr, year or years.

Table 2.29 Cessation of chewing of areca nut products (including betel quid) without tobacco and risk of oral cancer – case–control studies

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Ko et al. (1995) Taiwan (China)	Patients at a medical centre in Kaohsiung, southern Taiwan (China)	Hospital-based matched case–control study in 1992–1993 Case group: 107 patients with oral cancer with diagnosis confirmed by histopathology Control group: 200 age- and sex-matched controls consisting of non-carcinoma patients treated during the same period Chewers chewing ≥ 1 quid daily for ≥ 1 yr were defined as current chewers Confounding factors adjusted for in the multivariate analysis included education level, occupation, alcohol consumption, cigarette smoking, residence, marriage status, religion, ethnicity, and dietary habits	Oral cancer	Non-chewers: 31/153 Current chewers: 71/42 Former chewers: 5/5	1.0 (ref) 6.9 (3.1–15.2) 4.7 (0.9–22.7)	Information on duration of cessation was lacking Insufficient statistical power because of too few former chewers
Thomas et al. (2007) Papua New Guinea	Cases were patients with oral cancer hospitalized in 6 hospitals, and controls were those related to someone admitted to the same hospitals	Case–control study in 1985–1987 Case group: 143 patients with first diagnosis of clinically apparent oral squamous cell carcinoma Control group: 477 controls were those admitted or related to someone admitted to the same hospital Frequency-matching was performed on age, sex, and geographical location Confounding factors in the multivariate analysis included age, sex, province, residence, income, education level, and frequency of smoking	Oral cancer	Non-chewers: 2/9 Current daily chewers: 124/375 Current occasional chewers: 8/37 Former chewers: 9/56 Ever-chewers: 141/468	1.0 (ref) 1.29 (0.25–6.51) 0.98 (0.17–5.74) 0.57 (0.10–3.28) 1.10 (0.22–5.51)	This study had an extremely high prevalence of ever betel quid chewing

Table 2.29 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Lee et al. (2012) Taiwan (China)	Patients with carcinoma on the upper aerodigestive tract to gastrointestinal tract at 2 medical centres in Kaohsiung, southern Taiwan (China)	Multicentre case–control study in 2001–2007 Case group: Of the enrolled patients with cancer, 810 with oral cancer and 231 with pharyngeal cancer Control group: 2250 age- and sex-matched controls selected from the same hospital during the same period. Confounding factors in the multivariate analysis included sex, age, ethnicity, education level, drink-years of alcohol consumption, pack-years of cigarette smoking, and consumption of vegetables and fruits	Oral cancer and pharyngeal cancer	Oral cancer: Non-chewers: 136/2002 Current chewers: 450/160 Former chewers: 224/88 Pharyngeal cancer: Non-chewers: 55/2002 Current chewers: 147/160 Former chewers: 29/88	 1.0 (ref) 16.7 (12.1–23.0) 15.3 (10.6–22.0) 1.0 (ref) 9.3 (6.1–14.2) 3.5 (2.0–6.1)	Information on duration of cessation was lacking The possibility of reverse causation is a concern The pharyngeal cancer group included oropharyngeal and hypopharyngeal cancers

Table 2.29 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Wu et al. (2016) Taiwan (China)	Male patients at one medical centre in Tainan City	Hospital-based case–control study in 2010–2014 Case group: 487 male patients aged ≥ 20 yr with a new diagnosis of head and neck cancer. Of them, 313 had oral cancer and 119 had oro-hypopharyngeal cancer Control group: 617 male controls matched to the cases on age and from the same department as the cases but undergoing surgery for non-cancerous disease not related to alcohol consumption, betel quid use, or smoking, and without history of cancer diagnosis Confounding factors in the multivariate analysis included age, education level, cigarette smoking (pack-year categories), and alcohol consumption (frequency)	Oral cancer and pharyngeal cancer	Oral cancer: Non-chewers: 67/446 Current chewers: 113/66 Former chewers: 133/105 Duration of cessation (yr): Current chewers: 113/66 0.0–9.9: 67/59 10.0–19.9: 48/23 ≥ 20: 15/25 Per year of cessation Oro- and hypo-pharyngeal cancer: Non-chewers: 31/446 Current chewers: 45/66 Former chewers: 43/105 Duration of cessation (yr): Current chewers: 45/66 0.0–9.9: 28/56 10.0–19.9: 9/23 ≥ 20: 6/25 Per year of cessation	 1.0 (ref) 8.05 (5.10–12.71) 6.43 (4.25–9.73) 1.0 (ref) 0.72 (0.44–1.17) 1.42 (0.77–2.61) 0.34 (0.16–0.73) 0.976 (0.952–1.001) 1.0 (ref) 4.80 (2.57–8.99) 2.87 (1.61–5.13) 1.0 (ref) 0.74 (0.39–1.42) 0.63 (0.24–1.61) 0.26 (0.09–0.78) 0.967 (0.933–1.001)	Control group selected from the otolaryngology and stomatology departments may not be representative of the general population in their risk of oro- and hypopharyngeal cancer

Table 2.29 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	Cancer end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Meta-analysis						
Gupta et al. (2022)	4 case–control studies	Tobacco smoking was adjusted for in all the studies, and alcohol consumption was adjusted for in all studies except one	Oral cancer	Non-chewers Former chewers Current chewers	1.0 (ref) 5.61 (2.24–14.04) 7.89 (3.90–15.98)	Most studies included only or predominantly male participants. The duration of cessation for defining former chewers was > 1 yr in one study and > 6 months in one study; two studies did not mention this aspect

CI, confidence interval; OR, odds ratio; ref, reference; yr, year or years.

≥ 1 year. Compared with never-chewers, the OR for the risk of oral cancer in former chewers was lower (4.7; 95% CI, 0.9–22.7) than that in current chewers (6.9; 95% CI, 3.1–15.2). [The Working Group calculated that the OR for oral cancer in former chewers versus current chewers was 0.68 (95% CI, 0.12–3.79). The Working Group noted three limitations: (i) selecting controls from the ophthalmology and physical check-up departments may have a tendency to enrol few chewers, and this selection bias may lead to overestimation of the risk of oral cancer for current chewers and former chewers; (ii) many confounders may have required adjustment; and (iii) few former chewers led to insufficient statistical power.]

In a hospital-based case–control study in Papua New Guinea (Thomas et al., 2007), daily chewing of betel quid resulted in the highest RR of oral cancer (OR, 1.29; 95% CI, 0.25–6.51) compared with occasional chewing (OR, 0.98; 95% CI, 0.17–5.74) and with former chewing (OR, 0.57; 95% CI, 0.10–3.28). [The Working Group calculated an OR for oral cancer in former chewers compared with current chewers of 0.44 (95% CI, 0.04–4.73). There were very few never-chewers (the reference group): 1.4% (2 of 143) in the case group and 1.9% (9 of 477) in the control group. In addition, because controls were selected from patients who had a diagnosis unrelated to oral cancer but potentially related to other betel quid-related diseases, this may lead to underestimation of the risk of oral cancer.]

A multicentre case–control study was conducted in Taiwan (China) to assess the effect of consumption of betel quid without tobacco on the risk of aerodigestive tract cancers at different anatomical sites, with adjustment for age, ethnicity and education level (Lee et al., 2012). Compared with never-chewers, the OR for the risk of oral cancer in former chewers was 15.3 (95% CI, 10.6–22.0) and in current chewers was 16.7 (95% CI, 12.1–23.0). For pharyngeal cancer (including oropharyngeal and hypopharyngeal cancers), the estimated ORs were 3.5 (95% CI, 2.0–6.1) for former chewers and 9.3 (95% CI, 6.1–14.2) for current chewers, compared with never-chewers. [The Working Group calculated that the OR for former chewers versus current chewers was 0.92 (95% CI, 0.61–1.39) for oral cancer and 0.38 (95% CI, 0.20–0.70) for pharyngeal cancer. Because this is a hospital-based case–control study with study participants recruited from patients, the possibility that patients quit chewing after knowing the diagnosis of oral cancer cannot be ruled out.]

In another hospital-based case–control study to investigate the association between betel quid chewing and the risk of HNC at different sites (Wu et al., 2016), 487 male cancer patients and 617 age- and sex-matched controls were enrolled in 2010–2014. Information obtained by questionnaire included data for the three categories of betel quid chewers – current, former (stopped > 6 months ago), and never. Time since cessation for the former chewers was expressed as a continuous variable in years or an ordinal variable in 10-year categories (0–9.9 years, 10–19.9 years, and ≥ 20 years). For oral cancer, the OR for former chewers (6.43; 95% CI, 4.25–9.73) was lower than that for current chewers (8.05; 95% CI, 5.10–12.71) compared with never-chewers. [This resulted in a 20% reduction in RR of oral cancer (OR, 0.80; 95% CI, 0.51–1.24), calculated by the Working Group.] A significant trend with duration of cessation was noted, with a RR reduction that was significant for ≥ 20 years of betel quid cessation for oral cancer (OR, 0.34; 95% CI, 0.16–0.73) and for pharyngeal cancer (including oropharyngeal and hypopharyngeal cancers) (OR, 0.26; 95% CI, 0.09–0.78), but the risk was still greater than that in never-chewers. Each year of cessation of betel quid chewing was associated with a 2.4% RR reduction (OR, 0.976; 95% CI, 0.952–1.001) for oral cancer and a 3.3% RR reduction (OR, 0.967; 95% CI, 0.933–1.001) for pharyngeal cancer. [The strength of this study is to address a non-linear dose–response relationship between the amount and the duration

of chewing and duration of cessation associated with HNC including oral cancer and pharyngeal cancer by using a spline regression method. The study has three main limitations. First, because the control group was selected from the otolaryngology and stomatology departments, the source population for the control group may be different from that for the case group; thus, selection bias cannot be ruled out. Second, recall bias in the retrieval of information on chewing behaviour cannot be avoided. Third, the findings may have been affected by other unadjusted confounding factors, such as occupation, although age, education level, alcohol consumption, and smoking had been controlled for.]

The recently published meta-analysis (Gupta et al., 2022) combined data on chewing areca nut without tobacco from the four case–control studies described above. The risk estimate for oral cancer in former chewers (meta-RR, 5.61; 95% CI, 2.24–14.04) was lower than that in current chewers (7.89; 95% CI, 3.90–15.98) compared with never-chewers. [The analysis could not report on duration of cessation, because information on duration of cessation is lacking for most of the published studies.]

(ii) Evidence from primary data analyses

See Table 2.30.

Data on duration of cessation and age at quitting from three prospective cohort studies and one case–control study were available for primary analysis by the Working Group. The three cohort studies were derived from three community-based integrated screening programmes for common cancer types (including oral cancer) in three cities in Taiwan (China): Keelung, Changhua, and Tainan, representing the northern, central, and southern parts of the country, where areca nut is consumed unripe and without tobacco. Information on demographic characteristics, education level, duration and frequency of smoking, alcohol consumption, age at quitting, and duration of cessation was collected at entry. The study design and implementation were very similar across studies. The three cohorts were followed up over time to ascertain OPMDs and oral cancers. The case–control study was derived from one of the studies in Taiwan (China) on OPMDs and oral cancer in collaboration with the United States National Cancer Institute.

Results from three cohort studies showed statistically significant trends of reduced risk of oral cancer with an increase in time since quitting ($P_{trend} < 0.01$). The most significant reduction was noted for ≥ 20 years of quitting in Keelung and Tainan and for ≥ 10 years of quitting in Changhua. The RR reductions per year of cessation were all statistically significant: 6.7% (95% CI, 1.9–11.2%) in Keelung, 2.6% (95% CI, 0.8–4.4%) in Changhua, and 2.3% (95% CI, 0.1–4.5%) in Tainan. With respect to age at quitting, the younger the age at quitting, the lower the risk of oral cancer, as shown by the significant increasing trends per year of advancing age at quitting, 13% in Keelung and 3% in Changhua, and a non-significant 1% in Tainan. Notably, the results from the two cohort studies in the areas where the prevalence of areca nut chewing is high – Tainan (in the southern part) and Changhua (in the central part) – showed that quitting areca nut chewing before age 40 years led to a significant reduction in the risk of oral cancer. [For each cohort, a time-dependent Cox regression model was used to consider dynamic change of duration of quitting during follow-up. Relevant confounding factors have been well controlled to avoid recall bias.]

For the case–control study, analyses restricted to ever-chewers resulted in a statistically significant relative reduction in risk per year of cessation, estimated as 7% (95% CI, 5–9%).

[The Working Group also performed a meta-analysis that combined the information on the three user categories from the observational studies presented in Table 2.29 and Table 2.30. Former chewers had a statistically significantly

Table 2.30 Cessation of chewing of areca nut products (including betel quid) without tobacco and risk of oral cancer – primary data analyses performed by the Working Group

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Keelung, Taiwan (China)	Community-based integrated screening study for residents aged 30 yr in Keelung, northern Taiwan (China) (KCIS programme) 121 714 people were enrolled, and 372 oral cancers were ascertained during follow-up	Prospective cohort study People attending the KCIS programme in 1999–2018. This cohort was followed up to ascertain incident oral cancer by linking with the national cancer registry in Taiwan (China) until 31 December 2018 A time-dependent Cox regression model was used to consider dynamic change of duration of cessation during follow-up Confounding factors adjusted for were age, sex, education level, smoking (never, < 10, 10–19.9, 20–29.9, and ≥ 30 pack-years), and alcohol consumption (never, ever, current)	Oral cancer	Never-chewers: 245/110 555	1.00 (ref)	This is a large-scale community-based screening programme with long-term follow-up for the outcome of incident oral cancer and information on betel quid chewing in Keelung, where the prevalence of betel quid chewing is lower than in other parts of Taiwan (China)
				Former chewers: 57/4757	2.40 (1.68–3.42)	
				Current chewers: 64/4034	3.02 (2.16–4.22)	
				Per year of cessation of betel quid chewing	0.933 (0.888–0.981)	
				Duration of cessation (yr):		
				Current chewers	1.00 (ref)	
				< 10: 39/2410	1.78 (1.09–2.90)	
				10–20: 5/973	0.75 (0.43–1.31)	
				≥ 20: 1/465	0.16 (0.04–0.67)	
				Never-chewers	0.32 (0.23–0.45)	
					P_{trend} < 0.0001	
				Per year of age at quitting	1.13 (1.05–1.22)	
				Age at quitting (yr):		
				Current chewers	1.00 (ref)	
				< 40: 18/2364	0.72 (0.42–1.22)	
				40–49: 14/986	0.82 (0.43–1.75)	
				≥ 50: 13/497	1.48 (0.80–2.76)	
				Never-chewers	0.34 (0.24–0.47)	

Table 2.30 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Changhua, Taiwan (China)	Community-based integrated screening study for residents aged 30 yr in Changhua, central Taiwan (China) (CHCIS programme) 92 246 people were enrolled in the CHCIS cohort, and 311 oral cancers were ascertained during follow-up	Prospective cohort study People enrolled in 2005–2014 were used to assess the impact of cessation of betel quid chewing on risk of oral cancer. This cohort was followed up to ascertain incident oral cancer by linking with the national cancer registry until 31 December 2018 Exposures include current chewers, former chewers, and never-chewers; time in years since cessation measured in continuous years Confounding factors adjusted for in the Cox regression model included age, sex, education level, smoking (never, < 10, 10–19.9, 20–29.9, and ≥ 30 pack-years), and alcohol consumption (never, seldom, 1–2 per wk, 3–5 per wk, and daily drinkers) A time-dependent Cox regression model was used to consider dynamic change of duration of cessation during follow-up	Oral cancer	Never-chewers: 109/83 537 Former chewers: 119/5149 Current chewers: 82/2921 Per year of cessation of betel quid chewing Duration of cessation (yr): Current chewers < 10: 61/1992 10–20: 28/1617 ≥ 20: 17/1119 Never-chewers Per year of age at quitting Age at quitting (yr): Current chewers < 40: 25/1793 40–49: 37/1590 ≥ 50: 53/1673 Never-chewers 	1.00 (ref) 3.86 (2.73–5.46) 4.77 (3.31–6.89) 0.974 (0.956–0.992) 1.00 (ref) 1.09 (0.75–1.59) 0.65 (0.44–0.97) 0.59 (0.37–0.93) 0.22 (0.15–0.31) P_{trend} = 0.0142 1.03 (1.00–1.05) 1.00 (ref) 0.64 (0.40–1.00) 0.87 (0.58–1.29) 0.84 (0.58–1.21) 0.21 (0.14–0.30) P_{trend} = 0.3255	This is a large-scale community-based screening programme, in an area with a high prevalence of betel quid chewing

Table 2.30 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Tainan, Taiwan (China)	Community-based integrated screening study for residents aged 40 yr in southern Taiwan (China) (CIS programme) 125 977 people were enrolled in the CIS cohort, and 417 oral cancers were ascertained during follow-up	Prospective cohort study People enrolled in 2004–2009 were used to assess the impact of cessation of betel quid chewing on risk of oral cancer. This cohort was followed up to ascertain incident oral cancer by linking with the national cancer registry until 31 December 2018 Exposures include current chewers, former chewers, and never-chewers; time in years since cessation measured in continuous years Confounding factors adjusted for in the Cox regression model included age, sex, education level, smoking (never, < 10, 10–19.9, 20–29.9, and ≥ 30 pack-years), and alcohol consumption (never, seldom, 1–2 per wk, 3–5 per wk, and daily drinkers)	Oral cancer	Never-chewers: 232/116 869	1.00 (ref)	This is a large-scale community-based screening programme in an area with a higher prevalence of betel quid chewing
				Former chewers: 85/4838	3.20 (2.40–4.29)	
				Current chewers: 99/3806	4.34 (3.27–5.77)	
				Per year of cessation of betel quid chewing	0.977 (0.955–0.999)	
				Duration of cessation (yr):		
				Current chewers:	1.00 (ref)	
				< 10: 48/2263	0.88 (0.58–1.36)	
				10–20: 23/1316	0.83 (0.57–1.12)	
				≥ 20: 6/797	0.40 (0.22–0.75)	
				Never-chewers	0.22 (0.17–0.30)	
					P_{trend} = 0.0068	
				Per year of age at quitting	1.01 (0.99–1.04)	
				Age at quitting (yr):		
				Current chewers:	1.00 (ref)	
				< 40: 17/1598	0.51 (0.30–0.86)	
				40–59: 55/2741	0.80 (0.58–1.12)	
				≥ 60: 12/474	0.91 (0.49–1.69)	
				Never-chewers	0.22 (0.18–0.31)	
					P_{trend} = 0.2362	

Table 2.30 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; US NCI Taiwan (China) OPMD and oral cancer study	Study conducted in 4 hospitals in Taiwan (China): NTUH Taipei, CMUH Taichung, CGMH-Linkou, and CGMH-Kaohsiung	Hospital-based case–control study, with recruitment of controls, patients with oral cancer or OPMDs (primarily leukoplakia and some OSF) Controls were frequency-matched to case group (OPMDs and cancer) on age (5-year groups), sex, study site, ever-smoking, and ever-chewing Participants recruited in 2013–2021; recruitment of controls and OPMD cases is continuing This analysis (conducted in November 2021) included 388 controls and 549 cancer cases. Analyses were restricted to ever-chewers. Multinomial logistic regression models (cancer vs control) were adjusted for age, sex, education level (≤ vs > high school), smoking duration and intensity, alcohol consumption (drinks per week), and chewing duration and intensity. Primary analyses based on duration of cessation (as a continuous, linear variable and a categorical variable: quit ≤ 2 yr, 2–5 yr, 5–10 yr, 10–15 yr, and ≥ 15 yr)	Oral cancer	Per year of cessation of betel quid chewing Duration of cessation (yr): Current chewers: 241/158 < 2: 43/12 2–5: 63/32 5–10: 86/64 10–15: 45/35 ≥ 15: 72/87	0.93 (0.91–0.95) P_{trend} < 0.001 1.00 (ref) 2.08 (1.06–4.09) 1.09 (0.67–1.76) 0.67 (0.44–1.01) 0.49 (0.28–0.84) 0.21 (0.12–0.37) P_{trend} < 0.001	

CGMH, Chang Gung Memorial Hospital; CHCIS, Changhua Community-Based Integrated Screening; CI, confidence interval; CIS, Community-Based Integrated Screening; CMUH, China Medical University Hospital; KCIS, Keelung Community-Based Integrated Screening; NTUH, National Taiwan University Hospital; OPMDs, oral potentially malignant disorders; OSF, oral submucous fibrosis; ref, reference; US NCI, United States National Cancer Institute; vs, versus; wk, week; yr, years or years.

lower risk of oral cancer (OR, 0.79; 95% CI, 0.68–0.94) compared with current chewers.]

(b) Studies on OPMDs

(i) Evidence from the published literature

See Table 2.31.

Shiu et al. (2000) established a leukoplakia cohort, which consisted of 435 patients diagnosed at one medical centre in Taiwan (China) in 1988–1998. To assess the role of betel quid chewing, tobacco smoking, and alcohol consumption on the risk of leukoplakia, the case group consisted of 100 patients with leukoplakia randomly selected from the cohort, and the control group consisted of 100 patients with periodontal disease diagnosed in the same period and at the same medical centre, matched on age, sex, and date of diagnosis. After adjustment for smoking and alcohol consumption, with never-chewers as the reference group, the OR for leukoplakia in former chewers (2.38; 95% CI, 0.34–16.75) was much lower than that in current chewers (17.43; 95% CI, 1.94–156.27). [The Working Group noted the extremely wide CIs. The Working Group estimated the OR for former chewers as 0.14 (95% CI, 0.007–2.73) compared with current chewers. This study enrolled the control group from the same medical centre in the same period as the case group to ensure that both groups were from the same catchment area. Information was collected via telephone survey for both groups, instead of using medical chart review; this can avoid differential misclassification bias because in the medical charts, information on betel quid chewing, tobacco smoking, and alcohol consumption was more likely to be queried at diagnosis of leukoplakia than at diagnosis of periodontal disease. However, the use of a control group derived from patients diagnosed with periodontal disease may be a concern.]

Lee et al. (2003) reported on a hospital-based case–control study on OPMDs, including leukoplakia and OSF, conducted in 1994–1995 in Taiwan (China). Information on betel quid chewing, smoking, and alcohol consumption was collected via a structured questionnaire through in-person interview. A total of 219 cases (leukoplakia or OSF) and 876 controls were included. The OR for leukoplakia in former chewers compared with never-chewers (7.1; 95% CI, 2.3–21.5) was significantly lower than that in current chewers (22.3; 95% CI, 11.3–43.8). Similar findings were reported for OSF. [The Working Group calculated the ORs for former chewers compared with current chewers as 0.32 (95% CI, 0.09–1.10) for leukoplakia and 0.30 (95% CI, 0.06–1.58) for OSF. The fact that oral examination was not performed in the control group may have introduced bias. It is not clear whether the estimates were adjusted for tobacco smoking and alcohol consumption.]

A case–control study in Papua New Guinea (Thomas et al., 2008) reported an OR for former chewers that was lower than that for occasional chewers and daily chewers compared with never-chewers. [The Working Group noted that a limitation of this study was the extremely high prevalence of ever betel quid chewing; the proportion of never-chewers was only 0.5% (1 of 197) in the case group and 6.9% (89 of 1282) in the control group.]

A cross-sectional community screening study for oral cancer conducted in four Indigenous communities in Taiwan (China) in people aged ≥ 35 years in 2005 reported on the association between betel quid chewing and leukoplakia and OSF (Yang et al., 2010). The ORs for former chewers were lower than those for current chewers for leukoplakia in women (OR, 7.8; 95% CI, 3.8–16.0 vs 15.6; 95% CI, 8.3–29.4), for OSF in men (OR, 13.5; 95% CI, 3.8–48.7 vs 22.9; 95% CI, 7.3–71.7), and for OSF in women (OR, 9.3; 95% CI, 3.3–26.0 vs 13.0; 95% CI, 5.2–32.6). In contrast, for leukoplakia in men, ORs for former chewers were similar to those for current chewers (OR, 6.7; 95% CI, 3.2–13.9 vs 6.6; 95% CI, 3.5–12.3). [The ORs calculated for former chewers compared with current chewers were 0.50 (95% CI, 0.20–1.22) for leukoplakia in women, 0.59 (95% CI, 0.12–2.96)

Table 2.31 Cessation of chewing of areca nut products (including betel quid) without tobacco and risk of OPMDs – observational studies

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	OPMDs end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Case–control studies						
Shiu et al. (2000) Taiwan (China)	Patients with leukoplakia in a medical centre in Taipei and their matched controls from patients with periodontal disease	Case–control study Case group: 100 cases randomly selected from a cohort of 435 patients with leukoplakia diagnosed in 1988–1998 Control group: 100 controls with periodontal disease diagnosed in the same period and medical centre, matched to cases on age at diagnosis (± 3 yr), sex, and date of diagnosis Confounding factors in the multivariate analysis included cigarette smoking and alcohol consumption	Leukoplakia	Leukoplakia: Never-chewers Current chewers Former chewers	 1.0 (ref) 17.43 (1.94–156.27) 2.38 (0.34–16.75)	All cases and controls were interviewed via telephone survey, to avoid information bias between the 2 groups
Lee et al. (2003) Taiwan (China)	Patients at a medical centre in Kaohsiung and their sex- and age-matched controls from residents in the Greater Kaohsiung area	Matched case–control study conducted in 1994–1995 Case group: 219 patients with leukoplakia (n = 125) or OSF (n = 94) newly diagnosed and histologically confirmed Control group: 876 sex- and age-matched controls from 1864 household units Confounding factors in the multivariate analysis included education level and occupation	Leukoplakia and OSF	Leukoplakia: Never-chewers: 28/390 Current chewers: 91/88 Former chewers: 6/22 OSF: Never-chewers: 11/302 Current chewers: 78/62 Former chewers: 5/12	 1.0 (ref) 22.3 (11.3–43.8) 7.1 (2.3–21.5) 1.0 (ref) 40.7 (16.0–103.7) 12.1 (2.8–51.9)	People in the control group did not receive an oral inspection. This might result in a biased estimate Data on duration of cessation for former chewers were not available Not clear whether adjusted for tobacco smoking and alcohol consumption

Table 2.31 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	OPMDs end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Thomas et al. (2008) Papua New Guinea	People aged ≥ 18 yr from 2 census divisions (East Coast Kara Nalik and South Lavongai) of New Ireland Province	A case–control study nested in a cross-sectional study in 1992 Case group: 197 patients with identified leukoplakia Control group: 1282 controls ascertained in the cross-sectional study with no evidence of oral squamous cell carcinoma, leukoplakia, leukoedema, erythroplakia, or commissural ulceration Confounding factors in the multivariate analysis included age, sex, census division, and smoking	Leukoplakia	Never-chewers: 1/89 Former chewers: 7/149 Occasional chewers: 26/256 Daily chewers: 163/788	1.0 (ref) 1.4 (0.2–13.0) 6.1 (0.8–48.7) 5.0 (0.6–39.1)	Extremely high prevalence of ever betel quid chewing. The proportion of never-chewers was 0.5% (1 of 197) in the case group and 6.9% (89 of 1282) in the control group
Cross-sectional studies						
Yang et al. (2010) Taiwan (China)	Community oral cancer screening programme in 4 Indigenous communities and 1 remote island in Pingtung County	Cross-sectional study in 2005 Participants aged ≥ 35 yr, including 494 Indigenous men and 892 Indigenous women The proportion of ever-chewers was 11.0%, and the proportion of current chewers was 24.4%. The corresponding proportions were 13.4% and 29.4% for men and 14.6% and 35.2% for women Confounding factors in the multivariate analysis included sex, age, tobacco smoking, and alcohol consumption	Leukoplakia and OSF	Leukoplakia: 224 Men: Non-chewers Current chewers Former chewers Women: Non-chewers Current chewers Former chewers OSF: 89 Men: Non-chewers Current chewers Former chewers Women: Non-chewers Current chewers Former chewers	 1.0 (ref) 6.57 (3.51–12.28) 6.70 (3.21–13.99) 1.0 (ref) 15.63 (8.31–29.39) 7.78 (3.77–16.04) 1.0 (ref) 22.86 (7.28–71.73) 13.53 (3.76–48.65) 1.0 (ref) 13.03 (5.21–32.62) 9.32 (3.34–26.00)	Information on duration of cessation was lacking

Table 2.31 (continued)

Reference Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	OPMDs end-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Yen et al. (2011) Taiwan (China)	Community-based integrated screening programme in Keelung City	Cross-sectional study in 2003–2008 79 940 participants aged ≥ 20 yr; 502 OPMDs Confounding factors in the multivariate analysis included metabolic syndrome, age, sex, education level, tobacco smoking, and alcohol consumption	OPMDs	OPMD cases (% lesion):		Estimates provided in the publication were crude ORs
				Non-chewers: 256 (3.4%)	1.0 (ref)	
				Current chewers: 180 (80%)	25.25 (20.77–30.69)	
				Former chewers: 64 (25%)	7.43 (5.64–9.80)	
				Adjusted		
				Non-chewers	1.0 (ref)	
				Current chewers	[9.2 (7.2–11.8)]	
				Former chewers	[2.8 (2.0–3.8)]	
				Former vs current	[0.30 (0.22–0.43)]	

CHCIS, Changhua Community-Based Integrated Screening; CI, confidence interval; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; ref, reference; vs, versus; yr, year or years.

for OSF in men, and 0.72 (95% CI, 0.20–2.58) for OSF in women. This cross-sectional study did not provide information on duration of cessation, and there is a possibility of reverse causation, which may explain the results obtained in men.]

The cross-sectional study of Yen et al. (2011) reported data on the risk of OPMDs in the Keelung Community-Based Integrated Screening (KCIS) programme in Taiwan (China) in 2003–2008 in former and current chewers of betel quid aged ≥ 20 years. [The Working Group recalculated adjusted ORs: the estimate for former chewers versus never-chewers (2.8; 95% CI, 2.0–3.8) was lower than that for current chewers versus never-chewers (9.2; 95% CI, 7.2–11.8), giving an OR for former chewers versus current chewers of 0.30 (95% CI, 0.22–0.43). When former chewers were stratified by duration of quitting, an inverse dose–response relationship was noted between time since quitting and the risk of OPMDs, with ORs of 0.39 (95% CI, 0.27–0.56) for < 10 years of quitting, 0.22 (95% CI, 0.10–0.44) for 10–19 years of quitting, and 0.19 (95% CI, 0.06–0.60) for ≥ 20 years of quitting. This large-scale community-based screening programme provided stable estimates. This was an integrated screening programme that targeted multiple neoplasms and chronic diseases, for which information on general health was queried, instead of focusing on oral health; therefore, participants were less likely to avoid answering questions about smoking and betel quid chewing. In addition, all disease status data were measured or collected upon screening activity. Information bias on both independent covariates and disease outcomes could be ruled out.]

(ii) Evidence from primary data analyses

See Table 2.32.

Data on duration of cessation and age at quitting from three prospective cohort studies and one case–control study were available for primary analysis by the Working Group. The same three cohorts (in Keelung, Changhua, and Tainan) and the case–control study in Taiwan (China) are described above for oral cancer (see Section 2.3.5(a)(ii)).

The three cohort studies reported statistically significant trends of reduced RR of OPMDs with increasing time since quitting ($P_{trend} < 0.001$). The most significant reduction was noted for ≥ 5 years of abstinence in Keelung and Changhua and for ≥ 2 years of abstinence in Tainan. All the risk reductions per year of cessation were statistically significant: 3.5% (95% CI, 2.3–4.6%) in Keelung, 3.2% (95% CI, 2.2–4.2%) in Changhua, and 0.8% (95% CI, 0.5–1.1%) in Tainan. With respect to age at quitting, the younger the age at quitting the lower the risk of OPMDs, with significant RR reductions per year of younger age at quitting of 2% in Keelung, 1.4% in Changhua, and 2% in Tainan. When comparing former versus current chewers, cessation of chewing areca nut products without tobacco led to a significant reduction in the risk of OPMDs in all three cohorts.

In the case–control study in southern Taiwan (China), analyses restricted to ever-chewers resulted in a statistically significant 5% reduction in RR per year of cessation (OR, 0.95; 95% CI, 0.93–0.98).

The Working Group performed a meta-analysis combining information on the three user categories (current chewers, former chewers, and never-chewers) from the observational studies presented in Table 2.31 and Table 2.32. Former chewers had a statistically significantly lower risk of OPMDs (OR, 0.55; 95% CI, 0.39–0.72) compared with current chewers.]

2.3.6 HPV16 infection

Three types of HPV vaccines are currently available: a bivalent vaccine, a quadrivalent vaccine, and a nonavalent vaccine (Schiller and Lowy, 2012; Arbyn and Xu, 2018). All three target HPV16, the type that causes most HPV-associated oral and oropharyngeal cancers. HPV vaccines are prophylactic (i.e.

Table 2.32 Cessation of chewing of areca nut products (including betel quid) without tobacco and risk of OPMDs – primary data analyses performed by the Working Group

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Keelung, Taiwan (China)	Community-based integrated screening study for residents aged 30 yr in Keelung, northern Taiwan (China) (KCIS) 124 353 people were enrolled in the CHCIS cohort, and 3630 OPMDs were ascertained during follow-up	Prospective cohort study People attending the KCIS programme in 1999–2020 were used to assess the impact of quitting betel quid chewing on risk of OPMDs. This cohort was followed up to ascertain incident OPMDs by linking with the national cancer screening registry until 31 December 2020 Patients with oral cancer and people with a diagnosis of OPMD before the prevalent screen in KCIS were excluded Exposures included current chewers, former chewers, and never-chewers; age at cessation and time in years since cessation measured in continuous years Further details on this study are given in Table 2.30. Confounding factors adjusted for in the Cox regression model included age, sex, education level, smoking (never, < 10, 10–19.9, 20–29.9, and ≥ 30 pack-years), and alcohol consumption (never, ever, current) A time-dependent Cox regression model was used to consider dynamic change of duration of cessation during follow-up	OPMD (leukoplakia, erythroleukoplakia, erythroplakia, OSF, oral verrucous hyperplasia)	Never-chewers: 2124/111 486 Former chewers: 611/4273 Current chewers: 844/3229 Per year of cessation of betel quid chewing Current chewers Duration of cessation (yr): < 2: 116/503 2–5: 132/797 5–10: 97/800 10–15: 70/656 ≥ 15: 78/718 Never-chewers Per year of age at quitting Current chewers Age at quitting (yr): < 40: 275/2174 40–49: 149/850 ≥ 50: 69/444 Never-chewers	1.00 (ref) 2.22 (2.00–2.46) 3.43 (3.11–3.78) 0.965 (0.954–0.977) 1.00 (ref) 0.83 (0.57–1.19) 0.83 (0.65–1.07) 0.75 (0.61–0.91) 0.66 (0.55–0.81) 0.50 (0.42–0.60) 0.29 (0.26–0.32) P_{trend} < 0.0001 1.02 (1.01–1.04) 1.00 (ref) 0.58 (0.50–0.67) 0.77 (0.64–0.92) 0.77 (0.60–0.99) 0.30 (0.27–0.33) P_{trend} = 0.0073	This is a large-scale community-based screening programme, in an area where the prevalence of betel quid chewing is lower than in other parts of Taiwan (China) Because of the repeated attendance to screening, both prevalent and incident OPMDs were included in the analysis

Table 2.32 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Changhua, Taiwan (China)	Community-based integrated screening study for residents aged 30 yr in Changhua, central Taiwan (China) (CHCIS programme) 37 327 people were enrolled in the CHCIS cohort, and 1548 OPMDs were ascertained during follow-up	Prospective cohort study People enrolled in 2005–2014 were used to assess the impact of cessation of betel quid chewing on risk of oral cancer and OPMDs. This cohort was followed up to ascertain incident oral cancer by linking with the national cancer until 31 December 2018 Further details on this study are given in Table 2.30	OPMD (leukoplakia, erythroleukoplakia, erythroplakia, OSF, oral verrucous hyperplasia)	Never-chewers: 646/28 997	1.00 (ref)	Large-scale community-based screening programme in an area where the prevalence of betel quid chewing is higher than in other parts of Taiwan (China)
				Former chewers: 440/4429	1.55 (1.35–1.78)	
				Current chewers: 460/2315	2.57 (2.24–2.95)	
				Per year of cessation of betel quid chewing	0.968 (0.958–0.978)	
				Current chewers	1.00 (ref)	
				Duration of cessation (yr):		
				< 2: 55/314	0.84 (0.43–1.64)	
				2–5: 79/613	0.90 (0.65–1.25)	
				5–10: 85/739	0.64 (0.50–0.80)	
				10–15: 82/960	0.65 (0.52–0.80)	
				≥ 15: 111/1434	0.53 (0.44–0.64)	
				Never-chewers	0.39 (0.34–0.45)	
					$P_{trend} < 0.0001$	
				Per year of age at quitting	1.014 (1.002–1.026)	
				Current chewers:	1.00 (ref)	
				Age at quitting (yr):		
				< 40: 134/1564	0.55 (0.45–0.67)	
				40–49: 154/1348	0.67 (0.55–0.80)	
				≥ 50: 144/1439	0.61 (0.50–0.74)	
				Never-chewers	0.39 (0.34–0.45)	
					$P_{trend} = 0.4313$	

Table 2.32 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; community-based integrated screening, Tainan, Taiwan (China)	Community-based integrated screening study for residents aged 40 yr in Tainan, southern Taiwan (China) (CIS programme) 125 977 people were enrolled in the Tainan cohort, and 1584 OPMDs were ascertained during follow-up	Prospective cohort study People attending the CIS programme in 2004–2009 were used to assess the impact of cessation of betel quid chewing on risk of oral cancer and OPMDs. This cohort was followed up for incident oral cancer by the using national cancer registry until 31 December 2018 Patients with oral cancer were excluded Exposures included current chewers, former chewers, and never-chewer; time in years since cessation measured in continuous years Adjustments for confounding factors in this study are given in Table 2.29	OPMD (leukoplakia, erythroleukoplakia, erythroplakia, OSF, oral verrucous hyperplasia)	Never-chewers: 745/95 516	1.00 (ref)	Large-scale community-based screening programme in an area where the prevalence of betel quid chewing is the highest in Taiwan (China)
				Former chewers: 363/4761	1.94 (1.69–2.23)	
				Current chewers: 471/3767	2.95 (2.39–3.37)	
				Per year of cessation of betel quid chewing	0.992 (0.989–0.995)	
				Current chewers	1.00 (ref)	
				Duration of cessation (yr):		
				< 2: 63/464	1.06 (0.81–1.37)	
				2–5: 73/801	0.76 (0.59–0.97)	
				5–10: 66/912	0.62 (0.48–0.79)	
				10–15: 57/941	0.57 (0.43–0.75)	
				≥ 15: 60/1117	0.61 (0.47–0.80)	
				Never-chewers	0.34 (0.30–0.38)	
					P_{trend} < 0.0001	
				Per year of age at quitting	1.02 (1.00–1.03)	
				Current chewers:	1.00 (ref)	
				Age at quitting (yr):		
				< 40: 105/1566	0.54 (0.44–0.67)	
				40–49: 156/1693	0.76 (0.64–0.92)	
				≥ 50: 83/1392	0.75 (0.59–0.95)	
				Never-chewers	0.33 (0.29–0.38)	
					P_{trend} = 0.0002	

Table 2.32 (continued)

Study Location	Study population	Study design, study period, number of participants, information on betel quid chewing, and confounders considered	End-point	Exposure category Number of cases/ controls	OR (95% CI)	Comments
Unpublished; US NCI Taiwan (China) OPMD and oral cancer study	Study conducted in 4 hospitals in Taiwan (China): NTUH Taipei, CMUH Taichung, CGMH-Linkou, and CGMH-Kaohsiung	Hospital-based case–control study, with recruitment of controls, patients with oral cancer or OPMDs (primarily leukoplakia and some OSF) This analysis (conducted in November 2021) included 388 controls and 1468 OPMDs Further details on this study are given in Table 2.29 on oral cancer	OPMD	Per year of cessation of betel quid chewing	0.95 (0.93–0.97) $P_{trend} < 0.001$	
				Current chewers: 743/158	1.00 (ref)	
				Duration of cessation (yr):		
				< 2: 106/12	1.78 (0.95–3.34)	
				2–5: 142/32	0.87 (0.57–1.34)	
				5–10: 167/64	0.48 (0.34–0.69)	
				10–15: 11/35	0.49 (0.31–0.79)	
				≥ 15: 199/87	0.30 (0.19–0.47) $P_{trend} < 0.001$	

CGMH, Chang Gung Memorial Hospital; CHCIS, Changhua Community-Based Integrated Screening; CI, confidence interval; KCIS, Keelung Community-Based Integrated Screening; NTUH, National Taiwan University Hospital; OPMDs, oral potentially malignant disorders; OR, odds ratio; OSF, oral submucous fibrosis; ref, reference; US NCI, United States National Cancer Institute; yr, year or years.

vaccination prevents future acquisition of infection) and not therapeutic (i.e. vaccination does not enable clearance of prevalent infection) (Schiller and Lowy, 2012; Arbyn and Xu, 2018). The key effector mechanism of vaccine efficacy is through the generation of systemic immunoglobulin G (IgG) antibody responses against the HPV L1 protein (Schiller and Lowy, 2012; Arbyn and Xu, 2018).

The HPV vaccines have been shown to be safe, highly efficacious, and highly effective in preventing infection with vaccine-targeted HPV types (at the cervix, vagina, vulva, anus, penis, and oral cavity), anogenital warts, and HPV-associated precancer end-points (at the cervix, vagina, vulva, anus, and penis), and to result in population-level reductions in the incidence of cervical cancer (Drolet et al., 2019; Lei et al., 2020; Kjaer et al., 2021).

There is currently no empirical evidence that prophylactic HPV vaccination results in a reduction in the incidence of oral or oropharyngeal cancer or in the incidence of OPMDs. This lack of evidence arises from the recency of the introduction of HPV vaccines (in 2006 for women and 2011 for men in most countries) as well as the current recommendations to vaccinate young people (the routine recommendation is for vaccination before sexual debut until age 12–14 years and for catch-up vaccination until age mid-20s in some countries) (WHO, 2019). Because the latency interval between the acquisition of oral or oropharyngeal HPV16 infection and the development of HPV-associated oral or oropharyngeal cancer spans several decades, many more years of observation would be needed for prophylactic HPV vaccination of both sexes to result in a reduction in incidence of oral cancer or oropharyngeal cancer (Gillison et al., 2015).

However, there is a compelling scientific rationale that HPV vaccination would reduce the incidence of HPV-associated oral or oropharyngeal cancer in the future. First, several observational studies have shown that the prevalence of oral or oropharyngeal infection with vaccine-targeted HPV types (including HPV16) is 83–93% lower in vaccinated individuals than in unvaccinated individuals (Herrero et al., 2013; Chaturvedi et al., 2018; Schlecht et al., 2019). Second, emerging evidence indicates herd protection from HPV vaccination in the population with reduced prevalence of oral or oropharyngeal HPV infection in unvaccinated individuals (Chaturvedi et al., 2019; Mehanna et al., 2019). Third, there is a strong analogy from other anatomical sites with respect to vaccine efficacy and effectiveness; analogous decreases in HPV infections, HPV-associated precancers, and cancers at other anatomical sites (cervix, vagina, vulva, anus, and penis) have been consistently reported in vaccinated individuals and populations.

Future reductions in the incidence of HPV-associated oral cancer and oropharyngeal cancer will depend on the extent of female and male vaccination coverage in men and women, as well as achieved levels of herd immunity in a country or region. In regions with high levels of female and/or gender-neutral vaccination coverage, it would be expected that over the next 10–15 years HPV vaccination will result in population-level reductions in the incidence of HPV-associated oral cancer and oropharyngeal cancer.

2.4 Preventive dietary agents

This section presents the available evidence on dietary agents that may have a protective effect on the development of oral cancer and OPMDs.

2.4.1 Preventive dietary agents for the development of oral cancer

(a) Coffee

The 2018 WCRF report (WCRF/AICR, 2018) concluded that there is "limited suggestive evidence" that consumption of coffee may decrease the risk of oral cancer.

Studies on the association between coffee drinking and the incidence of oral cancer has been reviewed in two meta-analyses (Miranda et al., 2017; He et al., 2020) and one pooled analysis (Galeone et al., 2010) (Supplementary Table S2.33, web only; available from https://publications.iarc.fr/617). Miranda et al. (2017) calculated a meta-OR for the association between oral cancer and coffee drinking of 0.82 (95% CI, 0.58–1.16) using data from one cohort study (Ren et al., 2010) and five case–control studies (Franco et al., 1989; Franceschi et al., 1992; Pintos et al., 1994; Bundgaard et al., 1995; Radoï et al., 2013b). He et al. (2020) included all the studies that were part of the meta-analysis by Miranda et al. (2017), alongside with one additional case–control study and one cohort study. They calculated a meta-OR for oral cancer (OR, 0.79; 95% CI, 0.40–1.58) for coffee drinkers using data from four case–control studies (Franco et al., 1989; Franceschi et al., 1992; Bundgaard et al., 1995; Radoï et al., 2013b). Galeone et al. (2010) provided a pooled analysis of nine case–control studies of the INHANCE cohort. They found a significant 54% reduction in RR for drinking > 4 cups per day versus none (OR, 0.46; 95% CI, 0.30–0.71).

(b) Tea

The evidence for the association between tea drinking and cancers of the mouth, pharynx, and larynx was considered limited by the WCRF reports, and no conclusion could be reached as to a protective or harmful effect (WCRF, 2016; WCRF/AICR, 2018).

Current evidence comes from a pooled analysis of cases and controls from 9 studies in the INHANCE consortium (Galeone et al., 2010), a meta-analysis of 14 case–control studies (Zhou et al., 2018), a meta-analysis of one cohort study and four case–control studies (Filippini et al., 2020), and one individual cohort study (Ren et al., 2010) (Supplementary Table S2.33, web only; available from https://publications.iarc.fr/617). These studies reported risk estimates for oral cancer associated with self-reported tea consumption taking into account major risk factors, including tobacco smoking and alcohol consumption.

The pooled analysis, which included study participants from France, Italy, Puerto Rico, Switzerland, and the USA, generated a non-statistically significant adjusted pooled estimate of risk of oral cancer associated with tea drinking of 1.06 (95% CI, 0.88–1.27); the estimate was slightly reduced when based on people drinking > 1 cup of tea per day (OR, 0.94; 95% CI, 0.68–1.29) (Galeone et al., 2010). In a meta-analysis of studies conducted in Brazil, China, Denmark, Egypt, France, India, and Italy that reported adjusted risk estimates for oral cancer, Zhou et al. (2018) generated an overall meta-estimate of risk of oral cancer associated with tea consumption (OR, 0.70; 95% CI, 0.61–0.81). In a dose–response analysis including 8 of the 14 case–control studies, the risk of oral cancer decreased by 6.2% per 1 cup increase per day (OR, 0.938; 95% CI, 0.922–0.955). [This study presented additional pooled risk estimates according to type of tea, geographical region, sex, and age group.]

In their more recent systematic review of green tea drinking and cancer, Filippini et al. (2020) reported a significant inverse association, with a meta-estimate of risk of oral cancer associated with consumption of green tea comparing the highest versus the lowest intake (meta-RR, 0.71; 95% CI, 0.62–0.82).

One cohort study in the USA (Ren et al., 2010) reported non-statistically significant inverse associations, after adjustment for important confounders, in the category of the largest number of cups of tea consumed (HR for ≥ 1 cup of hot tea per day, 0.75; 95% CI, 0.53–1.06; HR for ≥ 1 cup of iced tea per day, 0.89; 95% CI, 0.67–1.19; and HR for ≥ 5 cups of green tea per day, 0.44; 95% CI, 0.19–1.04).

(c) Fruits and vegetables

The preventive role of consumption of fruits and vegetables on risk of oral cancer has been investigated in a large pooled analysis of 22 case–control studies (Chuang et al., 2012), a meta-analysis of 15 case–control studies and one cohort study (Pavia et al., 2006), two cohort studies (Freedman et al., 2008; Maasland et al., 2015), and three additional case–control studies (Supplementary Table S2.33, web only; available from https://publications.iarc.fr/617).

The 2018 WCRF systematic review (WCRF/AICR, 2018) reported a limited–suggestive decrease in risk of oral cancer associated with "healthy dietary patterns" and with "greater intake of non-starchy vegetables".

In the pooled analysis, in which intake of fruits and of vegetables were standardized into frequency quartiles, the highest relative to the lowest consumption level conferred reduced risks of oral cancer for fruits (OR, 0.46; 95% CI, 0.38–0.56) and for vegetables (OR, 0.69; 95% CI, 0.61–0.79) (Chuang et al., 2012). Similarly, the meta-analysis found that each portion consumed per day of fruit (OR, 0.49; 95% CI, 0.39, 0.63) and of vegetables (OR, 0.43; 95% CI, 0.31, 0.59) showed significant reduction in the overall risk of oral cancer (Pavia et al., 2006).

The two cohort studies examined total consumption of fruits and vegetables. The cohort study in the USA, conducted in the late 1990s (Freedman et al., 2008), reported reduced risk of oral cancer with increasing total consumption of fruits and vegetables (HR per serving per 1000 calories, 0.93; 95% CI, 0.86–1.00). The cohort study in the Netherlands (Maasland et al., 2015), in which participants were enrolled in 1986 and followed up for 20 years, reported a reduction in RR with increasing frequency of total consumption of fruits and vegetables (RR per 2.5 g per day, 0.95; 95% CI, 0.92–0.99; $P_{trend} = 0.005$).

A significant reduction in RR associated with increasing consumption of specific fruits or vegetables was observed for raw green vegetables, citrus fruits, apples and pears, fresh tomatoes, and carotene-rich foods in one or several of three case–control studies conducted in Brazil (Franco et al., 1989; Galvão De Podestá et al., 2019) and India (Rajkumar et al., 2003). For non-starchy vegetables, the reduction in RR was modest (RR per 25 g per day, 0.95; 95% CI, 0.89–1.02 to RR per serving per 1000 calories, 0.84; 95% CI, 0.73–0.95) (WCRF, 2018).

(d) Dietary fibre

Evidence on the association between consumption of dietary fibre and oral cancer is available from one large pooled analysis of case–control studies and two individual cohort studies (Supplementary Table S2.33, web only; available from https://publications.iarc.fr/617).

The pooled analysis of 10 case–control studies in the INHANCE consortium (Kawakita et al., 2017), with 559 cases and 12 248 controls enrolled in Asia, Europe, and North America, reported reduced RR with consumption of dietary fibre; the pooled OR for the highest versus the lowest quintile category was 0.39 (95% CI, 0.29–0.52) for oral cancer and 0.54 (95% CI, 0.45–0.64) for oropharyngeal and hypopharyngeal cancers

combined. A cohort study from the NIH-AARP Diet and Health Study with 494 991 participants found a borderline association between dietary fibre intake and risk of oral cancer in women ($P_{trend} = 0.055$) but not in men ($P_{trend} = 0.576$) (Lam et al., 2011). A more recent cohort study from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial in the USA, with 101 700 participants enrolled in 1992–2001, reported a significant risk reduction for oral cavity and pharyngeal cancer with a dose–response relationship for total fibre intake, insoluble fibre intake, and soluble fibre intake (Kawakita et al., 2019).

(e) Mediterranean diet

People who adhere to the Mediterranean diet, which is based on consumption of olive oil in addition to frequent intake of fish and seafood, vegetables, fruits, and cereals, have been shown to have a strong inverse association between adherence to such a diet and risk of oral cancer (Trichopoulou and Lagiou, 1997; Petridou et al., 2002; Filomeno et al., 2014).

2.4.2 Preventive dietary agents for the development or progression of OPMDs

(a) Observational studies

In the mid-1990s, the Tata Institute of Fundamental Research (in Bombay, India) conducted several population-based case–control studies in three regions of India – Gujarat, Kerala, and Andhra Pradesh – to examine the role of food and nutrition on the progression of OPMDs (Gupta et al., 1998, 1999; Hebert et al., 2002; Supplementary Table S2.34, web only; available from https://publications.iarc.fr/617). A food frequency questionnaire was used that was specific to this population and was developed and validated for collecting dietary information needed to estimate exposure to 92 food items; the data included the frequency and quantity of consumption. All people interviewed were tobacco users, and most of the cases and controls had lower socioeconomic status. In Gujarat and Kerala, most of the cases were clinically diagnosed with leukoplakia or OSF, and in Andhra Pradesh most were diagnosed with palatal lesions due to reverse smoking. The study in Andhra Pradesh reported an OR for fibre intake (grams per day) of 0.96 (95% CI, 0.94–0.99; $P = 0.007$) (Hebert et al., 2002).

A case–control study in Sri Lanka (Amarasinghe et al., 2013), with cases of leukoplakia mainly, found a protective effect of consumption of > 2 portions per day of β-carotene-containing vegetables and fruits on development of OPMDs (Supplementary Table S2.34, web only; available from https://publications.iarc.fr/617). [The authors pointed to prevailing undernutrition in OPMD cases in this rural population with very low daily consumption of fruits and vegetables (< 2 portions per day).]

In a hospital-based case–control study in Rome, Italy (Cianfriglia et al., 1998), participants were interviewed about dietary habits, and the survey included questions on foods that are major sources of vitamin A and carotenoids. The consumption of foods rich in vitamin A – butter, eggs, liver, spinach, and carrots – in the control group was > 40% higher than that in the cases ($P < 0.001$). Specifically, the estimated mean retinol intake in the control group was significantly higher than that in the leukoplakia group (Supplementary Table S2.34, web only; available from https://publications.iarc.fr/617). Consumption of foods and nutrients rich in vitamins A, C, E, and B12, β-carotene, lycopene, folate, retinol, α-tocopherol, and antioxidant mineral zinc have been found to be protective against the development of OPMDs.

(b) Biochemical studies

Several biochemical investigations have studied the role of nutrients in blood (serum or plasma) in the development of OPMDs. All but one (cross-sectional) studies were of case–control

design; five were in India, two in Japan, one in Finland, and one in the Islamic Republic of Iran (Supplementary Table S2.35, web only; available from https://publications.iarc.fr/617).

In the studies in India, serum levels of vitamins A, C, E, and B12, β-carotene, folate, retinol, α-tocopherol, and antioxidant mineral zinc were lower in leukoplakia or OSF cases than in controls (Ramaswamy et al., 1996; Gupta et al., 2004; Bose et al., 2012; Basu and Guhan, 2015; Param et al., 2018). In men in Japan, serum levels of lycopene and β-carotene were significantly lower in leukoplakia cases than in healthy controls (Nagao et al., 2000). In the study in Finland, the prevalence of leukoplakia cases was significantly higher in a group with low plasma levels of ascorbic acid (≤ 25 µmol/L) (Tuovinen et al., 1992).

Two case–control studies reported on serum retinol and carotenoid levels in OLP cases (Nagao et al., 2001; Rezazadeh and Haghighat, 2021; Supplementary Table S2.35, web only; available from https://publications.iarc.fr/617). In the study in the Islamic Republic of Iran (Rezazadeh and Haghighat, 2021), neither parameter was found to be a risk factor for the development of OPMDs. In the study in Japan (Nagao et al., 2001), serum retinol levels were elevated in OLP cases. [The authors remarked that this could be due to changes in dietary habits by cases after the development of oral symptoms. In a subgroup analysis, serum lycopene levels were low in 4 cases with erosive lesions.]

Serum analysis of leukoplakia cases in several of the included studies showed that significantly low antioxidant vitamin status and low serum zinc levels could promote the development of OPMDs.

[The Working Group noted that 7-day food dairies recorded after the detection of an OPMD may be biased by the avoidance of certain foods because of new oral symptoms, especially in patients with OSF.]

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3. CESSATION OF SMOKELESS TOBACCO AND/OR ARECA NUT USE

3.1 Product definition and description

The term "smokeless tobacco" refers to a large variety of commercially available or non-commercially available products that contain tobacco as the principal constituent and that are used either orally (chewing, sucking, placing in the cheek or lip pouch, or drinking) or nasally, without combustion (IARC, 2007; Siddiqi et al., 2020). Areca nut is the seed of the fruit of the *Areca catechu* L. (Palmaceae) tree, a palm that is indigenous to South Asia (IARC, 2004). Smokeless tobacco and areca nut may be consumed separately or combined (Mehrtash et al., 2017).

Although in some publications the term "smokeless tobacco" may include products with tobacco and areca nut combined, this *Handbook* considers the following three product categories: (i) "smokeless tobacco", defined as smokeless tobacco not containing areca nut; (ii) "areca nut without tobacco"; and (iii) "areca nut with tobacco" (Table 3.1).

Smokeless tobacco (SLT) is available as a myriad of products. They vary substantially in their names and their use in each region; the greatest diversity is observed in South and South-East Asia. For example, these products are known as *khaini*, *zarda*, *naswar*, and *gul* in South-East Asia, as *chimó* and *rapé* in South America, as plug, snuff, and *snus* in the USA, Canada, and Mexico, and as *shammah* in the Arabian Peninsula. In Sweden and some other Nordic countries, the use of *snus*, a particular type of moist snuff, is still prevalent (Siddiqi et al., 2020; WHO FCTC and ICMR-NICPR, 2022).

Preparations of areca nut mixed with tobacco are widely available commercially, such as betel quid and gutka. Areca nut may also be consumed on its own, especially in South Asia in the form of *supari*, *paan masala*, betel quid without tobacco, *binglang*, or *kili* (IARC, 2004; Cruising Maldives, 2016).

Both SLT and areca nut have been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme (IARC, 2004, 2007, 2012). Multiple carcinogens have been identified in SLT, such as tobacco-specific *N*-nitrosamines, *N*-nitrosamino acids, volatile *N*-nitrosamines, and polycyclic aromatic hydrocarbons (IARC, 2012; Hecht and Hatsukami, 2022). Areca nut contains several alkaloids and tannins (polyphenols). Arecoline, which has been classified as possibly carcinogenic to humans (Group 2B), is the most abundant alkaloid and the key active ingredient in areca nut (IARC, 2012, 2021).

Table 3.1 Smokeless tobacco and areca nut products available in different regions

Product name	Alternative or colloquial names (if any) Location	Major constituents	Other features (mode of consumption, and processing and manufacturing)
Smokeless tobacco products (not containing areca nut)			
Chimó	WHO Region of the Americas (Venezuela, Colombia)	Tobacco leaf, baking soda, brown sugar, ashes from mamón tree	Oral (sucked, held in mouth) Cottage industry or manufactured commercially
Creamy snuff	Tobacco toothpaste Commonly used in WHO South-East Asia Region (India)	Tobacco, clove oil, glycerin, spearmint, menthol, camphor	Oral (applied to teeth and gums) Manufactured commercially
Dry snuff	Scotch snuff, snuff (USA, Canada, Germany), *taaba* (Burkina Faso), *snuif* (South Africa), *sneif* (Botswana, Lesotho, South Africa), *azǒ* (Benin), *simonte* (Kalunga community in Brazil), *tapkeer*, *tapkir*, *bajjar* (India)	Tobacco (fire-cured or air-cured, fermented, powdered), flavourings	Oral (sucked, held in mouth) or nasal Manufactured commercially
Moist snuff	Dip, spit tobacco (USA, Canada, Mexico) *Shammah*: *el-shama*, *bajeli*, *haradi*, *sharaci*, black *shammah* (Yemen), *al-shammah* (Saudi Arabia), *chemma* (Algeria)	Tobacco (air-cured or fire-cured), flavourings, inorganic salts, moisturizers, slaked lime, ash, black pepper, oil	Oral (sucked) Manufactured commercially
	Toombak: saute, *sute*, *ammari*, *saood* Commonly used in WHO Eastern Mediterranean Region (Sudan), WHO African Region (Chad)	Tobacco leaves (dried, fermented, ground, matured), sodium bicarbonate	Oral (sucked, held in mouth) or nasal Cottage industry and custom-made
Dissolvable tobacco	Dissolvables Commonly used in WHO Region of the Americas (USA)	Tobacco, moisturizers, preservatives, flavourings	Oral (sucked, held in mouth, dissolved) Manufactured commercially
Tobacco-based toothpaste or tooth powder	*Gudaku* Commonly used in WHO South-East Asia Region (India)	Tobacco powder, molasses, red soil, lime, water	Oral (applied to teeth and gums, teeth cleaning, held in mouth) Manufactured commercially and custom-made
	Gul or *gul manjan* Commonly used in WHO South-East Asia Region (India, Bangladesh)	Tobacco (fire-cured, fermented, powdered), molasses, unknown ingredients	
	Mishri or *masheri* Commonly used in WHO South-East Asia Region (India)	Tobacco (toasted on hot metal plate, powdered)	
	Tapkeer, *tapkir*, *bajjar* Commonly used in WHO South-East Asia Region (India)		
Iqmik	Blackbull, *dediguss* Commonly used in WHO Region of the Americas (USA, Alaska)	Tobacco (fire-cured), tree fungus ash or other ash derived from wood or bush	Oral (chewed) Custom-made
Khaini	*Chadha*, *sada*, *surti* (Nepal and neighbouring parts of India) Commonly used in WHO South-East Asia Region (India, Bangladesh, Nepal, Bhutan)	Tobacco leaves (coarsely cut, sun-dried, fermented), slaked lime	Oral (sucked, held in mouth) Manufactured commercially, cottage industry, and custom-made
Kiwam	*Qiwam*, *qimam*, *khiwam*, *kimam* Commonly used in WHO South-East Asia Region, WHO Eastern Mediterranean Region (Pakistan)	Paste of tobacco extract, spices (cardamom, saffron, aniseed), additives such as musk	Oral (chewed or held in mouth) Manufactured commercially

Table 3.1 (continued)

Product name	Alternative or colloquial names (if any) Location	Major constituents	Other features (mode of consumption, and processing and manufacturing)
Nass	*Naswar, niswar, nasway, nasvay* Commonly used in WHO Eastern Mediterranean Region (Pakistan, Islamic Republic of Iran, Afghanistan, United Arab Emirates), WHO African Region (South Africa), WHO European Region (Armenia, Kazakhstan, Kyrgyzstan, Uzbekistan, Poland, Slovakia)	Tobacco, ash, cotton or sesame oil, water, flavourings such as cardamom and menthol	Oral (chewed, sucked, held in mouth) Cottage industry and custom-made
Rapé	Commonly used in WHO Region of the Americas (Brazil)	Dried tobacco leaf, selected tree ashes, flavourings such as tonka bean, clove, cinnamon powder, and camphor	Nasal inhalation Cottage industry and custom-made
Red tooth powder	*Lal dant manjan* Commonly used in WHO South-East Asia Region (India)	Fine red tobacco powder, herbs, flavourings; in addition, ginger, pepper, and camphor may be used	Oral (teeth brushing, cleaning) Manufactured commercially
Snus	Commonly used in Nordic countries and some other European countries, WHO Region of the Americas (USA, Canada, Brazil), WHO African Region (South Africa)	Tobacco, moisturizers, sodium carbonate, salt, sweeteners, flavourings	Oral (held in mouth) Manufactured commercially
Tobacco leaf	*Sada pata*, *chadha* Commonly used in WHO South-East Asia Region (India, Bangladesh, Myanmar, Bhutan)	Tobacco leaf	Oral (chewed) Custom-made
	Hsey or *hsey wah* (Myanmar)	Dried raw tobacco leaves	
	Hsey me' (Myanmar)	Cured and roasted tobacco leaves	
	Hsey paung or *hnut hsey* (Myanmar)	Tobacco leaves treated with alcohol and honey	
Tobacco water	*Tuibur*, *hidakpha* Commonly used in WHO South-East Asia Region (India)	Tobacco smoke, water	Oral (sipped or gargled) Cottage industry and custom-made
Hsey paung yay or black water	Myanmar	Scented tobacco soaked in honey, lime juice, and water	
Zarda	*Dokta* Commonly used in WHO South-East Asia Region (India, Bangladesh, Myanmar, Nepal, Bhutan), WHO Eastern Mediterranean Region (Yemen)	Tobacco, lime, vegetable dyes, aromatic spices	Oral (chewed; sometimes chewed with areca nut or silver flecks) Manufactured commercially

Table 3.1 (continued)

Product name	Alternative or colloquial names (if any) Location	Major constituents	Other features (mode of consumption, and processing and manufacturing)
Chewing tobacco	Loose leaf, chew, chaw, spit tobacco Commonly used in WHO Region of the Americas (USA)	Tobacco leaf (air-cured), sugar, liquorice	Oral (chewed or held in mouth) Manufactured commercially
	Plug, chew, chaw, spit tobacco Commonly used in WHO Region of the Americas (USA, Canada)	Heavy-grade or cigar tobacco top leaves, immersed in liquorice or sugar, and pressed into a plug	Oral (chewed, sucked, held in mouth) Manufactured commercially
	Twist, chew, chaw, chewing tobacco Commonly used in WHO Region of the Americas (USA)	Tobacco, tobacco leaf extract, sweetener, flavourings	Oral (chewed, held in mouth)
	Paraky (rural Madagascar)		Oral (chewed) Manufactured mainly in cottage industry
	Hsey or *hsey-ywet kyee* (Myanmar)	Raw and cured tobacco	
	Hsey hmwe (Myanmar)	Other varieties of tobacco mixture with added fragrances	
	Bush tobacco, *pituri* or *mingkulpa* (Indigenous people in Australia)	Fresh or dry leaves of certain tobacco species, mixed with burned wood ash and chewed into a quid	Oral (sucked)
Areca nut products without tobacco			
Betel quid without tobacco	Southern China, Pacific Islands	Areca nut (fresh, unripe) alone or with lime	Oral (chewed) Cottage industry and custom-made: prepared by individual vendors for sale, or assembled at home by individual users
	Hunan Province (China)	Areca nut (dried, unripe) alone or with lime	
	South Asia	Areca nut (cured, ripe) alone or with lime	
	Taiwan (China), Hainan Island (China), Papua New Guinea, Pacific islands	Areca nut (fresh, unripe) with lime and betel leaves	
	Lao-hwa quid Taiwan (China), Papua New Guinea	Areca nut (fresh, unripe) with lime and betel inflorescence	
	Stem quid:		
	Taiwan (China)	Areca nut (fresh, unripe) with lime and betel stem	
	Guam (USA)	Areca nut (fresh, unripe) with betel leaves	
	South Asia	Areca nut (cured, ripe) with lime and betel leaves	
	Paan or *pan* (South Asia)	Areca nut (cured, ripe) with lime, an additional source of catechins, flavourings, betel leaves	
Paan masala	*Pan masala* Commonly used in WHO South-East Asia Region	Areca nut, slaked lime, catechu, flavourings, sweeteners	Oral (chewed) Manufactured commercially and cottage industry

Table 3.1 (continued)

Product name	Alternative or colloquial names (if any) Location	Major constituents	Other features (mode of consumption, and processing and manufacturing)
Areca nut	*Supari* (WHO South-East Asia Region, India), *doma khando* (Bhutan), *buah pinang* (Indonesia), *meeru bileygan'du* and *heera panna* (Maldives), *pugua* (Guam, USA), *binglang* (China) Federated States of Micronesia: *bu* (Yap), *bua* (Belau), *poc* (Pohnpei), *pu* (Chuuk) *Buai*, *dak* (Papua New Guinea), *pinang* (Malaysia), *puwak* (Sri Lanka), *gua* (Bangladesh), *mak* (Thailand), *kun-ywet* (Myanmar)	Areca nut	Oral (chewed raw, fermented, or ripened; held in mouth)
Kili	Commonly used in Maldives	Areca nut, betel, cloves, cardamom, sugar	Oral Cottage industry and custom-made: produced by individual vendors for sale in small homemade paper pouches
Areca nut products with tobacco			
Betel quid with tobacco	*Paan* or *pan* (India), *khilli pan* (Bangladesh) Commonly used in WHO South-East Asia Region, WHO Eastern Mediterranean Region, WHO Western Pacific Region	Tobacco, areca nut, slaked lime (calcium hydroxide), betel leaf, catechu (*Acacia catechu* tree extract)	Oral (chewed) Cottage industry and custom-made: prepared by individual vendors for sale, or assembled at home by individual users
Dohra	Commonly used in WHO South-East Asia Region (India)	Tobacco, areca nut, catechu, slaked lime, peppermint, cardamom	Oral (chewed) Custom-made: produced by individual vendors for sale
Gutka	Commonly used in WHO South-East Asia Region, WHO Eastern Mediterranean Region	Tobacco (sun-dried, finely chopped), areca nut, slaked lime, catechu, flavourings, sweeteners	Oral (chewed) Manufactured commercially and cottage industry
Mainpuri	*Kapoori* Commonly used in WHO South-East Asia Region (Uttar Pradesh, India)	Tobacco leaves (pieces), slaked lime, areca nut, flavourings (camphor, cloves)	Oral (chewed or held in mouth) Cottage industry and custom-made: produced by individual vendors for sale
Mawa	*Kharra* Commonly used in WHO South-East Asia Region (India)	Crushed tobacco leaves (sun-dried), areca nut (sun-cured), slaked lime	Oral (chewed) Cottage industry and custom-made: produced by individual vendors for sale
Tombol	Commonly used in WHO Eastern Mediterranean Region (Yemen)	Tobacco, areca nut, *noura*, slaked lime, catechu, *tombol* leaf	Oral (chewed, held in mouth) Custom-made

WHO, World Health Organization.

Compiled by the Working Group, with data from Atkinson et al. (1964); Ahluwalia and Duguid (1966); Gupta and Ray (2002); Gupta and Warnakulasuriya (2002); IARC (2004, 2012); Lim (2012); Blecher et al. (2014); Moghbel et al. (2016); Novais (2017); Buente et al. (2020); Gunjal et al. (2020); Joo et al. (2020); Siddiqi et al. (2020); WHO (2021a, b, c); WHO FCTC and ICMR-NICPR (2022).

3.2 Prevalence of consumption

3.2.1 WHO South-East Asia Region

There are almost 266 million adult users of SLT or areca nut with tobacco (184 million men and 83 million women) in the World Health Organization (WHO) South-East Asia Region; it is the WHO region with the highest prevalence of use of these products in adults (WHO, 2021a).

Estimates for all the countries in the WHO South-East Asia Region are given in Table 3.2. [Although several recent detailed publications are available on "smokeless tobacco" or "chewing tobacco" in the WHO South-East Asia Region, they have imprecise definitions of the products involved; also, the words "areca nut" or "betel quid" rarely appear. Therefore, it was not always possible to present quantitative information on the prevalence of use of the three important product categories, i.e. SLT alone, areca nut without tobacco, and areca nut with tobacco.]

Most of the countries in the region have reported a high overall prevalence (≥ 5%) of SLT use, ranging from 15.8% in Sri Lanka to 27.5% in Bangladesh, with a few exceptions, such as the Democratic People's Republic of Korea (0.0%) and Thailand (2.1%). The prevalence of SLT use is generally high in both men and women in most of the countries (WHO, 2021b). However, in several countries (e.g. Bangladesh, Indonesia, and Thailand), the prevalence of SLT use is slightly higher in women than in men (WHO, 2017, 2021b). Similar to the situation for adults, the WHO South-East Asia Region is the WHO region with the highest prevalence of SLT use in young people, with 4.2 million users (2.7 million boys and 1.5 million girls). Nepal has the highest reported prevalence of SLT use in adolescents (16.2%), followed by Timor-Leste (13.9%), Bhutan (12.5%), Maldives (6.2%), and Myanmar (5.7%). The prevalence of SLT use was higher in boys in all the countries, ranging from 1.4% in Indonesia to 19.7% in Nepal, except in Timor-Leste, which reported a slightly higher prevalence of SLT use in girls (14.8%) than in boys (12.2%) (WHO, 2021b). Such averages hide wide variations, given the cultural diversity of the region (Table 3.2).

In an extremely detailed global analysis of the prevalence of "chewing tobacco" in 1990–2019, unlike the trend for tobacco smoking, no significant decrease was noted in the trends of prevalence of SLT use in male or female individuals aged ≥ 15 years in countries in the WHO South-East Asia Region: Bangladesh, Bhutan, India, Myanmar, Nepal, and Sri Lanka (GBD 2019 Chewing Tobacco Collaborators, 2021). Some trends can also be interpolated from the repeated WHO Global Adult Tobacco Survey (GATS), which now includes data on SLT but not on use of areca nut products of any kind. For instance, the GATS India reported a significant decrease (–17.4%) in the percentage of current SLT users between 2009–2010 (25.9%) and 2016–2017 (21.4%) (TISS and MOHFW, 2017).

In the WHO South-East Asia Region, a common way of using tobacco is as an ingredient in betel quid (i.e. areca nut with tobacco) (see Section 3.1 and Table 3.1). Use of betel quid is an ancient practice; tobacco was added beginning in about 1600, and this is now done in many parts of South-East Asia, such as India, Bhutan, Myanmar, Nepal, and Sri Lanka (NCI and CDC, 2014). The largest variety of SLT and areca nut products are available in India, such as *khaini*, *gutka*, *zarda*, *gul*, *gudaku*, *mishri*, tobacco water, and snuff, to name a few. The GATS-2 reported the highest prevalence of use for *khaini* (11.2%), followed by *gutka* (6.8%), betel quid with tobacco (5.8%), and oral tobacco (*gul*, *mishri*, *gudaku*) (3.8%) (TISS and MOHFW, 2017). Products such as *gutka*, *khaini*, and *paan masala* have been manufactured commercially since 1975 (NCI and CDC, 2014). *Khaini* and *gutka* are also commonly used in Bangladesh (known as *khoinee*), Nepal, and Sri Lanka. In addition to chewable products, the above-mentioned SLT and areca nut with tobacco products administered through oral application,

Table 3.2 Prevalence of smokeless tobacco and areca nut use in adults and adolescents in the WHO South-East Asia Region

Country	Product type and/or most popular names	Prevalence of use (%)	Reference
Bangladesh	*Sada pata*[a], *zarda*[a], *gul*[a], *khoinee*[a], *gutka*[c], *gua*[b]	SLT: Adults: Overall: 27.5 Men: 26.9 Women: 28.1	WHO (2021b)
		Youth: Overall: 4.5 Boys: 5.9 Girls: 2.0	WHO (2021b)
		AN: 31 Three quarters of users chewed BQ with tobacco	Flora et al. (2012)
Bhutan	BQ (usually with tobacco[c], AN (called *doma khando*), *khaini*[a]	SLT: Adults: Overall: 19.7 Men: 26.5 Women: 11.0	WHO (2021b)
		Youth: Overall: 12.5 Boys: 17.0 Girls: 8.1	WHO (2021b)
India	*Khaini*[a], BQ (with and without tobacco)[b,c], *gutka*[c], *supari*[b], *mishri*[a], *gul*[a], *gudaku*[a]	SLT: Adults: Overall: 21.4 (199.4 million) Men: 29.6 Women: 12.8 AN with tobacco: 14.2 (95% CI, 13.5–14.9) Various products containing SLT alone or AN with tobacco: *Khaini*: 11.2 *Gutka*: 6.8 BQ with tobacco: 5.8 Oral tobacco (*gul*, *mishri*, *gudaku*): 3.8 *Paan masala* with tobacco: 2.8	TISS and MOHFW (2017); Singh et al. (2021); WHO (2021b)

Table 3.2 (continued)

Country	Product type and/or most popular names	Prevalence of use (%)	Reference
India (cont.)		SLT: Youth: Overall: 4.1 Boys: 4.6 Girls: 3.4	MOHFW and IIPS (2019)
		AN: ~23.9 (95% CI, 23.1–24.8) (223.79 million adults) National prevalence of use of plain AN products; lowest and highest prevalence among states Average % (statewise variation %): BQ without tobacco: 8.7 (0.3–64.9) *Paan masala* without tobacco: 4.8 (0.2–11.5) AN alone without tobacco: 8.0 (0.2–22.6)	Singh et al. (2021)
		Tribal/Indigenous people are at high risk. Of 2186 tribal households in South India, 47.6% reported daily use of BQ (with or without tobacco)	Sadath et al. (2022)
Indonesia	*Buah pinang*[b], *zarda*[a]	SLT: Men: 3.9 Women: 4.8	WHO (2017)
		SLT: Youth: Overall: 1.0 Boys: 1.4 Girls: 0.7	WHO (2021b)
		AN without tobacco: Women: 15.0 Men: 1.6 AN with tobacco: Women: 31.7 Men: 10.4	Lee et al. (2011)
Maldives	Chewing tobacco[a], snuff[a], dip[a], *supari*[b], *meeru bileygan'du*[b], *heera panna*[b]	SLT: Youth: Overall: 6.2 Boys: 9.2 Girls: 2.9	WHO (2020a, 2021b)
		SLT: Men: 8.5 Women: 4.2	WHO (2021b)

Table 3.2 (continued)

Country	Product type and/or most popular names	Prevalence of use (%)	Reference
Myanmar	*Hsey* or *hsey-ywet kyee*, *hsey* or *hsey wah*, *hsey me'*, *hsey paung* or *hnut hsey*, *hsey paung ya* or black water, *hsey hmwe*[a], *kun-ya*[b]	SLT: Youth: Overall: 5.7 Boys: 11.0 Girls: 1.5	WHO (2018, 2021b, c)
	Also, imported commercial products	SLT: Men: 58.9 Women: 18.2	WHO (2021b)
	BQ with tobacco[c], such as tobacco leaf, *hnut hsey*, *hsey paung*, chewing tobacco leaf, *kun-ywet*[b]	AN with tobacco: 84% of respondents in a survey in Yangon	Papke et al. (2020)
Nepal	*Khaini*[a], *gutka*[c], *zarda*[a], *paan masala*[b], snuff[a], *gul*[a], BQ with tobacco[c]	Lifetime BQ (with tobacco) chewing: Men: 43.6 Women: 34.9	Lee et al. (2011)
		SLT: Adults: Overall: 18.3 Men: 33.3 Women: 4.9	WHO (2021b)
		SLT: Youth: Overall: 16.2 Boys: 19.7 Girls: 12.9	WHO (2021b)
Sri Lanka	BQ with tobacco[c], *paan masala*[b], *mawa*[a], red tooth powder[a], *khaini*[a], tobacco powder[a], *zarda*[a], *gutka*[c], *puwak*[b]	SLT: Adults: Overall: 15.8 Men: 26 Women: 5.3	WHO (2021b)
		SLT: Youth: Overall: 2.4 Boys: 4.2 Girls: 0.5	WHO (2021b)

Table 3.2 (continued)

Country	Product type and/or most popular names	Prevalence of use (%)	Reference
Sri Lanka (cont.)		AN without tobacco: Men: 11.6 Women: 10.4 AN with tobacco: Men: 6.4 Women: 3.2	Lee et al. (2011)
		AN with or without tobacco: Varies by ethnicity and geography; in one province in 1029 subjects (64.6% Sinhalese, 34.9% Tamil, 0.5% other) aged > 30 years, prevalence of daily BQ chewing was 53.8%: 15.7% without tobacco and 47.4% with tobacco	Amarasinghe et al. (2018)
Thailand	*Zarda*[a], *mak*[b]	SLT: Adults: Overall: 2.1 Men: 1.5 Women: 2.7	WHO (2021b)
		SLT: Youth: Overall: 2.7 Boys: 4.1 Girls: 1.3	WHO (2021b)
Timor-Leste	*Bua*[b]	SLT: Youth: Overall: 13.9 Boys: 12.2 Girls: 14.8	WHO (2021b)
		SLT: Adults: Men: 20.9 Women: 0.2	WHO (2021b)

AN, areca nut; BQ, betel quid; CI, confidence interval; SLT, smokeless tobacco; WHO, World Health Organization.
[a] SLT alone.
[b] AN alone (without tobacco).
[c] AN with tobacco.
Compiled by the Working Group.

such as *gul*, *gudaku*, and *mishri*, are also widely prevalent in Bangladesh and Nepal.

Consumption of areca nut is deeply embedded in the social and cultural history of the entire WHO South-East Asia Region. The *Areca catechu* palm tree is indigenous to the Malay Peninsula and Sri Lanka, and cultivation has been widespread across South-East and South Asia for millennia (Gupta and Warnakulasuriya, 2002). Areca nut or its preparations without tobacco are known by various colloquial names across the region, such as *doma khando* in Bhutan, *supari* in India and Maldives, *buah pinang* in Indonesia, *meeru bileyn'd* and *heera panna* in Maldives, and *bua* in Timor-Leste (Table 3.1). Areca nut is the primary component of betel quid, which may also be consumed without tobacco. The GATS-2 India reported the prevalence of the various plain areca nut products: betel quid (8.7%), areca nut (8%), and *paan masala* (4.8%) (Singh et al., 2021). The multicountry Asian Betel-Quid Consortium study, in 2009–2010, reported a high prevalence of chewing betel quid (without tobacco) in the adult population in Indonesia (15% in women and only 1.6% in men) and Sri Lanka (11.6% in men and 10.4% in women) (Lee et al., 2011). The prevalence of use of common SLT and areca nut with tobacco products (*paan* and *gutka*) was recently reviewed (Niaz et al., 2017).

In summary, the WHO South-East Asia Region has the highest prevalence of SLT and areca nut use among all WHO regions, and a large variety of both SLT and areca nut products are consumed in this region.

3.2.2 WHO Western Pacific Region

Areca nut or betel quid with tobacco are the main products consumed in the WHO Western Pacific Region. Chewing of areca nut is deeply embedded in the social and cultural history of many parts of the region; it may be consumed on its own (known by various colloquial names across the region) or as a component of betel quid. Areca nut chewing is a very ancient custom in the Philippines, from where it gradually spread across the Western Pacific islands, as planting of the *Areca catechu* palm increased (NCI and CDC, 2014).

A significant geographical variation is noted both within and among the countries in this region; in and close to continental Asia, the habits overlap with those in the WHO South-East Asia Region, whereas further east, they tend to mimic the habits of Chinese origin. Both the nature of the habits and the subpopulations in which particular constituents of a betel quid are favoured vary widely, and these are not always adequately described in the literature. Also, in the WHO and Global Burden of Disease analyses conducted for these subpopulations, SLT use is frequently referred to as the sole habit distinguished from smoked tobacco use, with no or rare mentions of areca nut (Siddiqi et al., 2020; GBD 2019 Chewing Tobacco Collaborators, 2021). As an example of the cultural variations, in Taiwan (China) and Palau, unripe nuts are used in the betel quid, whereas in Guam (USA), white immature or red mature nuts are preferred. Unwrapped quid is preferred in Papua New Guinea and the Solomon Islands, whereas wrapped betel quid (in betel leaf) is consumed in Cambodia, Palau, and the Federated States of Micronesia. Also, the use of tobacco with areca nut or in a betel quid is not seen in all cultures in the WHO Western Pacific Region. The multicountry Asian Betel-Quid Consortium study, in 2009–2010, reported a prevalence of chewing betel quid (without tobacco) ranging from 3.6% in Malaysia to 23.9% in China in men and from 1.8% in China to 17.5% in Malaysia in women (Lee et al., 2011). Similarly, users in island countries of Melanesia are unlikely to add tobacco to the quid. Certain specific subpopulations in a few countries have a higher prevalence of use of areca nut and SLT products, such as South Asian immigrants in Australia, Fiji, and Singapore, and

Indigenous people in Australia (Kuek et al., 1990; Nambiar et al., 2020; Greenhalgh et al., 2022).

There are about 13.3 million users of SLT (11 million male and 2.3 million female) in the WHO Western Pacific Region; it is the WHO region with the lowest average prevalence of SLT use in adults (0.9% overall, 1.4% in men, and 0.3% in women) (WHO, 2021a). The WHO Western Pacific Region is socially, culturally, economically, politically, and ethnically diverse, containing both the world's most populous country, China, and the smallest territory in the world, Pitcairn Island (NCI and CDC, 2014). The prevalence of SLT use varies widely, ranging from 0.1% in women in China to 48.8% in women in Palau (WHO, 2020b, 2021b).

There are limited robust longitudinal epidemiological studies on the prevalence of use of these products, although estimates from many countries in this region are presented in Table 3.3. Based on the available information, 4 countries in the WHO Western Pacific Region have reported a high overall prevalence (≥ 5%) of SLT use; the prevalence was highest in Palau (44.4%), followed by the Marshall Islands (21.6%), the Federated States of Micronesia (11.4%), and Malaysia (10.9%) (WHO, 2020b, 2021b). The prevalence of SLT use is generally higher in men in most of the countries in the region (WHO, 2021b). However, countries such as Palau (48.8%), Cambodia (8.6%), and the Lao People's Democratic Republic (8.6%) have a significantly higher prevalence of SLT use in women than in men (WHO, 2020b, 2021b). The WHO Western Pacific Region is the WHO region with the lowest prevalence of SLT use in adolescents (aged 13–15 years), with 0.9 million users (0.6 million boys and 0.3 million girls), but the prevalence of use is significantly high in Kiribati (38.6%), the Federated States of Micronesia (16.0%), the Marshall Islands (14.9%), Palau (14.7%), and Papua New Guinea (12.2%) (WHO, 2021a, b). The prevalence of SLT use was higher in boys in most of the countries, ranging from 1.3% in Cambodia to 42.5% in Kiribati, except in three countries that reported a relatively higher prevalence of SLT use in girls – Palau (16.8%), Papua New Guinea (13.6%), and Tuvalu (3.3%) – than in boys (WHO, 2021b).

In the extremely detailed global analysis of the prevalence of "chewing tobacco" in 1990–2019, unlike the trend for tobacco smoking, no significant decrease was noted in the trends of prevalence of SLT use in male or female individuals aged ≥ 15 years in countries in the WHO Western Pacific Region: Cambodia, the Marshall Islands, and Palau (GBD 2019 Chewing Tobacco Collaborators, 2021). Increases in the prevalence have been reported in specific communities, such as South Asian immigrants in Australia and non-Chamorros in Guam (USA), whereas decreases have been seen in Indigenous people in Australia, and in a few other locations, such as Papua New Guinea, Singapore, Taiwan (China), and Viet Nam.

In summary, although the WHO Western Pacific Region has reported the lowest average prevalence of SLT use of all WHO regions, the prevalence of consumption of areca nut products is high and this practice is spreading further across the region.

3.2.3 WHO European Region

In recent years, mass migration patterns and commercial integration have affected the historical regional prevalence of use of SLT products, which are now widely available in the WHO European Region (IARC, 2007; NCI and CDC, 2014; WHO, 2017, 2019).

Table 3.4 provides data for countries for which the estimated prevalence of SLT use was ≥ 2% in adults. Overall, the prevalence of SLT use is low in the WHO European Region, with diverse geographical and subregional trends that are greatly influenced by cultural and migration patterns.

Table 3.3 Prevalence of smokeless tobacco and areca nut use in adults and adolescents in the WHO Western Pacific Region

Country or territory	Product type and/or most popular names	Prevalence of use (%)	Trends of prevalence Reference
Australia	Both tobacco and AN products[a,b,c] (South Asian immigrants)	SLT: Overall: 0.4 Men: 0.6 Women: 0.3 No national data on AN products	Increasing in immigrants WHO (2021b)
	Bush tobacco, *pituri* or *mingkulpa* (Indigenous people)	Chewing tobacco prevalence in Indigenous people in the Northern Territory (central Australia) in 1986–1987: Women: 61 Men: 20	Decreasing in Indigenous people Greenhalgh et al. (2022)
Cambodia	AN with tobacco[c]	AN with tobacco: Women: 12.8 Men: 1.7 SLT: Overall: 4.9 Men: 0.8 Women: 8.6	Decreased slightly Chher et al. (2018); Gunjal et al. (2020); WHO (2021b)
China	AN with or without quid[b], *binglang*[b]	AN prevalence in 11 046 individuals in Xiangtan City, Hunan Province: Overall: 1.2 Men: 0.6 Women: 0.6 AN without tobacco: Men: 23.9 Women: 1.9 SLT: Overall: 0.9 Men: 1.6 Women: 0.1	Tang et al. (1997); Lee et al. (2011); WHO (2021b)
Cook Islands	SLT, AN	SLT: Overall: 3 Boys: 3.8 Girls: 2.4	AN: although use is spreading rapidly, no data are available WHO (2021b)
Fiji	*Paan masala*[b] and other imported packaged ingredients (South Asians)	SLT: 14.2 AN or *paan masala*: 20	In Fijians of Indian descent in Suva aged ≥ 18 yr Nambiar et al. (2020)
Guam (USA)	AN with or without tobacco[c], *pugua*[b]	Adults (AN with tobacco): 46 Youth (*pugua*): 48 AN (5-yr prevalence): 11	AN: increased (in non-Chamorros) Paulino et al. (2017a)

Table 3.3 (continued)

Country or territory	Product type and/or most popular names	Prevalence of use (%)	Trends of prevalence Reference
Kiribati		SLT: Adults Overall: 4.2 Men: 7.6 Women: 1.4 Youth: Overall: 38.6 Boys: 42.5 Girls: 35.3	WHO (2021b)
Lao People's Democratic Republic	BQ[b,c], AN[b]	SLT: Overall: 4.3 Men: 0.5 Women: 8.6	WHO (2021b)
Malaysia	BQ with or without tobacco[b,c], *pinang*[b]	SLT: Adults: Overall: 10.9 Men: 20.4 Women: 0.8 Youth: Overall: 6.3 Boys: 8.2 Girls: 4.3 AN with tobacco: Women: 12.0 Men: 6.2 AN without tobacco: Women: 17.5 Men: 3.6	Lee et al. (2011); WHO (2020b, 2021b)
Marshall Islands		"Chewing tobacco": Men: 10.36 Women: 4.06 SLT: Adults: Overall: 21.6 Youth: Overall: 14.9 Boys: 18.9 Girls: 11.8	Increasing GBD 2019 Chewing Tobacco Collaborators (2021); WHO (2021b)

Table 3.3 (continued)

Country or territory	Product type and/or most popular names	Prevalence of use (%)	Trends of prevalence Reference
Micronesia (Federated States of)	*Bu*, *bua*, *poc*, *pu*[b], BQ[b,c]	AN: School students: 63.4 In families: 42 (from 3 in the Marshall Islands to 94 in Yap) AN with tobacco: 84 SLT: Adults: Overall: 11.4 Men: 22.4 Women: 3.0 Youth: Overall: 16.0 Boys: 20.0 Girls: 12.7	Oakley et al. (2005); Paulino et al. (2017b); WHO (2021b)
Mongolia		SLT: Overall: 8.2 Boys: 11.8 Girls: 4.5	WHO (2021b)
Palau	BQ with or without tobacco[b]	AN without tobacco: Men: 70 Women: 80 AN with tobacco: 80 SLT: Adults: Overall: 44.4 Men: 40.2 Women: 48.8 Youth: Overall: 14.7 Boys: 12.2 Girls: 16.8	Ysaol et al. (1996); WHO (2020b, 2021b)
Papua New Guinea	*Buai*[b], *dak*[b]	Chewing tobacco: Men: 40 Women: 18 SLT: Youth: Overall: 12.2 Boys: 10.9 Girls: 13.6	Decrease (slight) WHO (2021b); GBD 2019 Chewing Tobacco Collaborators (2021)

Table 3.3 (continued)

Country or territory	Product type and/or most popular names	Prevalence of use (%)	Trends of prevalence Reference
Singapore	*Paan*[b], *makan sirih*[b]	AN: 6.4	Decreased (AN); more common in Indian community Kuek et al. (1990); Lim and Pakiam (2020)
Solomon Islands	AN[b]	AN: 94 in a sample of 400 people aged 15–24 yr	Increased Quinn et al. (2017); Moore (2020)
Taiwan (China)	BQ with and without tobacco[b,c], *binglang*[b]	AN without tobacco (in the multicountry ABC study): Men: 10.7 Women: 2.5 AN: 0.3 in 429 108 participants from the Senior Citizen Health Examination in Taiwan (China) over 10 yr (2001–2010)	Decreased Lee et al. (2011); Tsou et al. (2022)
Tonga		SLT: Men: 5 Women: 2	GBD 2019 Chewing Tobacco Collaborators (2021)
Vanuatu		SLT: Overall: 5.2 Boys: 5.9 Girls: 4.6	WHO (2021b)
Viet Nam	AN[b]	Women: 6.7 (in Ho Chi Minh City)	Decreased Reichart and Nguyen (2008); Gunjal et al. (2020)

ABC, Asian Betel-Quid Consortium; AN, areca nut; BQ, betel quid; SLT, smokeless tobacco; WHO, World Health Organization; yr, year or years.

[a] SLT alone.

[b] AN alone (without tobacco).

[c] AN with tobacco.

Compiled by the Working Group.

Table 3.4 Countries with high prevalence of smokeless tobacco and areca nut use in adults in the WHO European Region[a]

Country or population	Product name or colloquial name	Prevalence of use (%)			Reference
		Men	Women	Overall	
Czechia	Snuff and chewing tobacco[b]	5.9	2.5	4.2	NCI and CDC (2014); WHO (2021b)
Denmark	*Snus*[b]	4.0	1.0	3.0	Siddiqi et al. (2020); WHO (2021b)
Estonia	Not reported	9.2	2.3	5.1	WHO (2021b)
Finland	*Snus*[b]	9.2	1.0	5.2	Siddiqi et al. (2020); WHO (2021b)
Germany	Dry snuff[b]	3.4	3.4	2.0	Agaku et al. (2014); NCI and CDC (2014)
Iceland	*Snus*[b]	8.7	3.5	6.6	Siddiqi et al. (2020); WHO (2021b)
Kyrgyzstan	*Naswar*[b]	10.1	0.1	5.2	Siddiqi et al. (2020); WHO (2021b)
Malta	Chewing tobacco[b]	5.5	1.5	3.5	Agaku et al. (2014); NCI and CDC (2014)
Norway	*Snus*[b]	25.0	10.0	18.0	Siddiqi et al. (2020); WHO (2021b)
Portugal	Not reported	4.4	1.1	2.7	Agaku et al. (2014)
Slovenia	Not reported	3.1	1.2	2.2	WHO (2021b)
Spain	Not reported	2.1	2.9	2.5	Leon et al. (2016)
Sweden	*Snus*[b]	22.0	6.0	14.0	Siddiqi et al. (2020); WHO (2020b)
Switzerland	Snuff and chewing tobacco[b]	4.2	1.2	2.7	NCI and CDC (2014); WHO (2017)
South Asian immigrants in the United Kingdom	*Paan*[c,d], *gutka*[d], *zarda*[d], *khaini*[b], *naswar*[b]	7.0	6.0	7.0	ASH (2019)
Uzbekistan	*Naswar*[b]	19.8	0.4	9.9	Siddiqi et al. (2020); WHO (2021b)
WHO European Region		1.9	0.4	1.1	WHO (2021a)

WHO, World Health Organization.

[a] Countries with a prevalence of smokeless tobacco and areca nut use of ≥ 2% are included in the table; countries with a prevalence of < 2% (Armenia, Austria, France, Hungary, Ireland, Italy, Kazakhstan, Poland, Slovakia, Turkmenistan, and the United Kingdom) have been excluded.

[b] Smokeless tobacco alone.

[c] Areca nut without tobacco.

[d] Areca nut with tobacco.

Compiled by the Working Group.

Population-specific studies describing the patterns and prevalence of SLT use were not available for several countries in the WHO European Region in which isolated SLT use had previously been reported (Leon et al., 2016). However, 34 of 53 countries (64.1%) presented data on SLT use in adults; the regional average prevalence was 1.1%, with a higher prevalence in men (1.9%) than in women (0.4%) (WHO, 2021a). Prevalence of SLT use was high in Estonia (5.1%), Finland (5.2%), Iceland (6.6%), Kyrgyzstan (5.2%), Norway (18%), Sweden (14%), and Uzbekistan (9.9%) and in South Asian immigrants in the United Kingdom (WHO, 2020b, 2021b). Four of these countries exceeded the global average prevalence of SLT use (6%) (WHO, 2021a). In the countries where the practice is highly prevalent, hotspots of high prevalence of SLT use by men are observed in subregions, including the Nordic countries and in populations in central Asia (Ansara et al., 2013; WHO, 2020b, 2021b).

The WHO European Region is the WHO region with the second-lowest prevalence of SLT use in adolescents (aged 13–15 years), after the WHO Western Pacific Region (WHO, 2021b). Based on data from 12 countries, the prevalence of SLT use in adolescents was 1.5% (1.8% in boys and 1.1% in girls) (WHO, 2021a). The lowest prevalence of SLT use in adolescents was observed in Belarus, Kazakhstan, and San Marino (0.6%), and the highest prevalence was observed in Poland (5.6%), followed by Latvia (5.3%), Czechia (4.7%), and Georgia (4.4%) (WHO Regional Office for Europe, 2020). These hotspots of high prevalence of SLT use by adolescents, such as Latvia, may be due to the geographical proximity to Sweden, where the prevalence of SLT use is one of the highest among countries in the WHO European Region (Leon et al., 2016). In the United Kingdom, evidence about SLT use in adolescents is limited (WHO Regional Office for Europe, 2020).

Few specific data are available about the spectrum of products used, which encompass commercial and mixed-use preparations, or their variation in terms of natural and chemical compositions (IARC, 2007; NCI and CDC, 2014; WHO, 2017, 2019). Table 3.4 shows a limited variation in terms of the products and their use in the WHO European Region. Regulations for the consumption of SLT vary widely within countries in this region (WHO, 2017); however, in the European Union (EU), SLT is regulated under the scope of the EU Tobacco Products Directive 2014/40/EU (European Parliament, 2014), which banned all tobacco products for oral use. Although most SLT products were banned by the European Council Directive in 1989, in western Europe the use of *snus*, a particular type of moist snuff (see Section 3.1), is still prevalent among Scandinavian people, living mostly in Norway and Sweden (which are exempted from the ban) as well as in other Nordic countries, such as Denmark, Finland, and Iceland (Council of the European Communities, 1989; IARC, 2007; Leon et al., 2016). Other SLT products such as chewing tobacco and dry snuff are also allowed for sale and marketing in the WHO European Region (Leon et al., 2016). Originally from India, *gutka* and *zarda* (see Section 3.1) are the most consumed products in the United Kingdom, where about 75% of Asian immigrants had already consumed them. Similarly, areca nut products are also often consumed within immigrant communities from Pakistan and Bangladesh, among others, living in other parts of the WHO European Region (IARC, 2004; Lechner et al., 2019; Siddiqi et al., 2020).

In summary, a relatively small range of SLT products is currently consumed in nearly half of the countries in the WHO European Region, with large regional and cultural variations.

3.2.4 WHO Region of the Americas

Despite the heritage of SLT as an early American product (Shafey et al., 2009), SLT use is not heavily culturally embedded in

Table 3.5 Countries with high prevalence of smokeless tobacco use in adults in the WHO Region of the Americas[a]

Country	Product name or colloquial name	Prevalence of use (%)[b]			Reference
		Men	Women	Overall	
Haiti	Not reported	N/A	3.1	N/A	WHO (2021b)
Paraguay	Not reported	3	1.6	2.3	WHO (2021b)
USA	Snuff[b], *snus*[b], *iqmik*[b], plug[b]	6.2	0.6	3.3	Siddiqi et al. (2020); WHO (2021b)
Venezuela	*Chimó*[b]	6.2	0.9	3.5	Siddiqi et al. (2020); WHO (2021b)
WHO Region of the Americas		2.5	0.3	1.4	WHO (2021a)

N/A, not available; WHO, World Health Organization.

[a] Countries with a prevalence of smokeless tobacco use of ≥ 2% are included in the table; countries with a prevalence of < 2% (e.g. Argentina, Barbados, Canada, Dominican Republic, and Grenada) have been excluded.

[b] Smokeless tobacco alone.

Compiled by the Working Group.

contemporary societies in the WHO Region of the Americas, and only limited data are available about the prevalence of SLT use in this region (IARC, 2007; NCI and CDC, 2014). Recent evidence on the patterns and prevalence of SLT use was not found for several countries in this region in which isolated SLT use had previously been reported (WHO, 2017, 2019). Although countries in this region have a markedly low overall prevalence of SLT use, there are several subregions, with wide population diversity and a potentially variable prevalence of SLT use (Ansara et al., 2013). Table 3.5 provides the overall prevalence of SLT use in some of the countries in the WHO Region of the Americas for which the estimated prevalence of SLT use was ≥ 2% in adults. The regional average prevalence was 1.4%, and overall the prevalence was higher in men (2.5%) than in women (0.3%) in this region (WHO, 2021a); however, in countries such as Argentina (0.2%), Barbados (0.6%), and Haiti (3.1%), the prevalence was higher in women. Hotspots of high prevalence of SLT use by men were identified in the USA (6.2%), Venezuela (6.2%), and Paraguay (3%) (WHO, 2017, 2021b).

The average prevalence of SLT use reported in adolescents was 2.6% (3.4% in boys and 1.7% in girls) (WHO, 2021a). A total of 27 countries in the WHO Region of the Americas reported SLT use in adolescents, of which Saint Vincent and the Grenadines (6.3%), Venezuela (5.1%), and Barbados (5.0%) had the highest prevalence (PAHO, 2018).

There is significant variation in terms of the products used in the subregions (Siddiqi et al., 2020; Table 3.1). For example, *chimó* is the most widely consumed product in Venezuela and Colombia, whereas *rapé* is more common in Brazil. In the USA, Canada, and Mexico, plug, snuff, and *snus* are the major oral SLT products, whereas *iqmik* is commonly consumed by Alaska Natives (Siddiqi et al., 2020; Table 3.5). Areca nut consumption is reported among the residents of Hawaii, with a low prevalence in young people (ever use of 3.1% in high school students; current use of 1.3% in middle school students and 2% in high school students) compared with a much higher prevalence in immigrants from the Federated States of Micronesia (20.6%) (Pobutsky and Neri, 2012).

In summary, a relatively small range of SLT or areca nut products are currently consumed by nearly 1.5% of the population of the WHO Region of the Americas.

Table 3.6 Countries with high prevalence of smokeless tobacco use in the WHO African Region[a]

Country	Product name or colloquial name	Prevalence (%) Overall (male; female)	Trends of prevalence[b]	Reference
Algeria	*Chemma* or *shammah*[c]	8.9 (17.3; 0.4)	Increasing (men), decreasing (women)	NCI and CDC (2014); Oudjehih et al. (2020); WHO (2021b)
Benin	*Azô*[c]	5.7 (8; 3.2)	Decreasing	Siddiqi et al. (2015); WHO (2020b)
Burkina Faso	*Taaba*[c]	8.9 (5.6; 11.7)	Unknown	NCI and CDC (2014); WHO (2021b)
Central African Republic	Snuff[c]	16.3 (17.3; 15.5)	Unknown	NCI and CDC (2014); WHO (2021b)
Comoros	Unknown	18.4 (19.5; 17.4)	Unknown	WHO (2021b)
Madagascar	*Paraky*[c]	17.3 (24.6; 9.6)	Unknown	Blecher et al. (2014); WHO (2021b)
Mozambique	Unknown	5.6 (2.5; 7.9)	Unknown	WHO (2021b)
Sierra Leone	Snuff[c], chewing tobacco[c]	7.8 (2.9; 12.1)	Decreasing (slightly)	Samai et al. (2011); WHO (2021b); Drope et al. (2022)
Togo	Unknown	3.6 (5.1; 2.2)	Unknown	WHO (2021b)

WHO, World Health Organization.
[a] Countries with a prevalence of smokeless tobacco and areca nut use of ≥ 5% (either overall or in males or females) are included in the table.
[b] Unknown: no comparable data over a time period to make a call on trend.
[c] Smokeless tobacco alone.

3.2.5 WHO African Region

There are an estimated 15 million adult users of SLT (8 million men and 7 million women) in the WHO African Region; it is the WHO region with the second-highest prevalence of SLT use in adults, after the WHO South-East Asia Region (WHO, 2021a). The prevalence of use varies widely, ranging from 0.1% in women in Eritrea and Senegal to 24.6% in men in Madagascar (WHO, 2021b). Of the 46 countries in the WHO African Region, only 8 countries (Algeria, Benin, Burkina Faso, Central African Republic, the Comoros, Madagascar, Mozambique, and Sierra Leone) had a moderate to high (≥ 5%) overall prevalence of SLT use (WHO, 2020b, 2021b).

The prevalence of SLT use is generally high in both male and female individuals in Burkina Faso, the Central African Republic, the Comoros, and Madagascar (WHO, 2021b; Table 3.6). The high overall prevalence (17.3%) of SLT use in Madagascar may be attributed to the large number of residents of South Asian origin (Mamudu et al., 2013; WHO, 2021b). In the Comoros, which has a high overall prevalence of SLT use, the prevalence of SLT use in women (17.4%) is the highest of the African countries (WHO, 2021b). However, in some countries with a relatively low overall prevalence (< 5%) of SLT use, use is reported predominantly in women (prevalence > 5%), such as Botswana and Cabo Verde. The prevalence of SLT use is much higher in men than in women in countries such as Algeria (17.3% vs 0.4%), Eritrea (11.6% vs 0.1%), and Madagascar (24.6% vs 9.6%) (WHO, 2021b; Table 3.6).

Information about the trends in prevalence of SLT use has been reported for few countries. The available data suggest a decreasing trend in SLT use in women in Algeria, from a reported prevalence of 0.8% in 2010 to a prevalence of 0.4% in 2017, whereas the estimated prevalence in men increased, from 9.8% in 2010 to 17.3% in 2017 (Oudjehih et al., 2020; WHO, 2021b). Recent data

from a 2016 survey in South Africa also show a marked decrease in the prevalence of SLT use in women, from 10.9% in 2003 to 1.3% in 2016, whereas the prevalence in men increased, from 2.4% in 2003 to 6.4% in 2016 (Siddiqi et al., 2015; WHO, 2021b).

Youth surveys have suggested an increased uptake of SLT use in adolescent boys and girls, even in countries with a relatively low prevalence of SLT use in adults, such as Botswana, Eswatini, Liberia, Malawi, Nigeria, Rwanda, South Africa, and Uganda (WHO, 2021b). In countries with a moderate or high overall prevalence of SLT use, such as Burkina Faso and Mozambique, SLT use is also common in adolescents, with a reported prevalence of 10.2% in Burkina Faso and 7.5% in Mozambique and not much difference between sexes (WHO, 2021b). In contrast, recent data from Madagascar suggest a very low prevalence of SLT use in adolescents (1.6%); this is an indicator that this practice is probably becoming unpopular there (WHO, 2021b).

The dominant SLT product type used in the WHO African Region is snuff (moist and dry) (see Table 3.1) (NCI and CDC, 2014). It is also locally known as *taaba* in Burkina Faso, *chemma* or *shammah* (moist snuff) in Algeria, *snuif* in South Africa, Botswana, and Lesotho, and *azô* in Benin (NCI and CDC, 2014; Oudjehih et al., 2020). The use of chewing tobacco is less common. However, *paraky* is mostly used in rural areas of Madagascar (Blecher et al., 2014), and use of betel quid without tobacco (areca nut) is common in a minority population of South Asian descent in some parts of South Africa and the United Republic of Tanzania (Bissessur and Naidoo, 2009; Bhat et al., 2010; NCI and CDC, 2014). SLT use through the nasal route in the form of dry snuff is still a common practice in some parts of the WHO African Region (Sinha et al., 2018a), but oral application remains more popular (Table 3.1). In 2005, Scandinavian-type *snus* was also introduced to the South African market, but data on its use have not been reported, possibly because there was little or no uptake by most South Africans (Tobacco Control Research Group, 2021).

3.2.6 WHO Eastern Mediterranean Region

There are an estimated 20.9 million adult users of SLT (17.7 million men and 3.2 million women) in the WHO Eastern Mediterranean Region (WHO, 2021a). The prevalence of SLT use varies widely, ranging from null in women in Egypt, Iraq, and Kuwait and in both men and women in the Syrian Arab Republic to 33.7% in men in Afghanistan (WHO, 2021b; Table 3.7). The prevalence of SLT use is generally high in adults in Afghanistan, Yemen, the Sudan, Pakistan, and Tunisia (WHO, 2020b, 2021b). In Afghanistan, the 2019 WHO STEPwise Approach to Surveillance (STEPS) survey showed an overall prevalence of SLT use of 19.3% (33.7% in men and 3.7% in women); it is the country with the highest percentage of SLT users in the WHO Eastern Mediterranean Region (WHO, 2021b). Although in this region SLT is consumed predominantly by men, Yemen has reported a substantial prevalence of use (5.9%) in women (WHO, 2021b; Table 3.7).

Information about trends in prevalence of SLT use is available for some countries in this region (Table 3.7). In Pakistan, in adult men the prevalence of SLT use decreased from 16.3% in 2012–2013 to 11.4% in 2014 and to 14.6% in 2017–2018, but in women it increased from 2.44% in 2012–2013 to 3.7% in 2014 and to 3.4% in 2017–2018 (Siddiqi et al., 2015; WHO, 2020b, 2021b). In the Sudan, the 2005 STEPS country report showed a prevalence of SLT use of 24.1% in men and 1% in women, but recent data from the 2016 STEPS survey revealed a decreasing trend in the prevalence of SLT use in both men (to 14.3%) and women (to 0.2%) (Siddiqi et al., 2015; WHO, 2021b). In Yemen, when comparing the recent Demographic and Health Survey 2013 data with the 2003 Individual Country Survey

Table 3.7 Countries with high prevalence of smokeless tobacco use in the WHO Eastern Mediterranean Region[a]

Country	Product name or colloquial name	Prevalence (%) Overall (male; female)	Trends of prevalence	Reference
Afghanistan	*Naswar* or *nass*[b]	19.3 (33.7; 3.7)	Unknown	WHO (2021b)
Pakistan	*Gutka*[c], *naswar*[b], *chalia* or *supari*[d], *paan*[c,d], *zarda*[c]	9[e] (14.6; 3.4)	Decrease (males) Increase (females)	Siddiqi et al. (2015); WHO (2020b, 2021b)
Sudan	*Toombak*[b], *saffa*[b], *saod*[b]	7.9 (14.3; 0.2)	Decrease	Siddiqi et al. (2015); Abakar et al. (2020); WHO (2021b)
Yemen	*Shammah*[b], *toombak*[b], *tombol*[c]	11.3 (17.0; 5.9)	Increase (males)	Siddiqi et al. (2015); Al-Tayar et al. (2017); WHO (2021b)

WHO, World Health Organization.
[a] Countries with a prevalence of smokeless tobacco and areca nut use of ≥ 5% (either overall or in males or females) are included in the table.
[b] Smokeless tobacco alone.
[c] Areca nut with tobacco.
[d] Areca nut and/or betel quid alone.
[e] Overall prevalence data were not provided in the data source; therefore, the estimate provided here was computed by the Working Group.

data, the percentage of male SLT users appears to have increased slightly (from 15.1% in 2003 to 17% in 2013), but the percentage of female SLT users seems to have remained almost stable (from 6.2% in 2003 to 5.9% in 2013) (Siddiqi et al., 2015; WHO, 2021b).

In the WHO Eastern Mediterranean Region, SLT use seems to be relatively less common in adolescents than in adults (WHO, 2021a). The prevalence in adolescents is highest in Djibouti (6.2%), followed by the occupied Palestinian territory (6%), Pakistan (5.3%), and Yemen (5.1%) (WHO, 2021b). A relatively low prevalence of SLT use in adolescents in the Sudan (4.9%) compared with that in adult men suggests that this practice is becoming unpopular there, or that there is a cultural tendency towards uptake in adulthood (Idris et al., 1998; WHO, 2021b).

The dominant product types used in the WHO Eastern Mediterranean Region are plain SLT, or areca nut mixed with tobacco (NCI and CDC, 2014). A variety of products are available in the region, of which the most common forms are betel quid with tobacco (*paan*), *naswar*, *chalia*/*supari*, and *gutka*. A study in Pakistan reported that in a group of male and female users of SLT or areca nut products, the prevalence of use of *naswar* (4.1%) was the highest, followed by *paan* (2.6%) (Abbas et al., 2014). The use of these products is also culturally acceptable in Afghanistan, predominantly a local product known as *naswar* or *nass*. In the Sudan, SLT is referred to as *toombak*, *saffa*, or *saod* (Abakar et al., 2020). In Yemen, some of the commonly used products are *shammah*, *tombol*, and *toombak* (Al-Tayar et al., 2017; Table 3.7; see Section 3.1).

3.2.7 Determinants of use

Both SLT and areca nut contain addictive substances; this explains their continued use despite the proven adverse health effects, including oral cancer (Sumithrarachchi et al., 2021). Therefore, to effectively eliminate these practices, it is imperative to understand the reasons that influence the initiation and continued use of these products. Whereas cigarette smoking has been widely studied because

it is the causative factor for many noncommunicable diseases (Bergen and Caporaso, 1999), studies on determinants of use of SLT and areca nut are fewer in comparison.

Multiple factors determine the initiation and continued use of SLT and areca nut, with an interplay between some of the factors. These determinants may be broadly grouped as (i) individual factors (knowledge and perceptions), (ii) social factors (sociodemographic, socioeconomic, and sociocultural), and (iii) environmental factors (Table 3.8) (Singh et al., 2016).

Identifying the individual, social, and environmental determinants of the initiation and continuation of SLT and areca nut use is required when planning programmes on awareness and cessation interventions for these established risk factors.

(a) Individual factors

Inculcating appropriate knowledge or raising awareness has the ability to induce a desired health-related behavioural change. Several studies have shown that knowledge levels and perceptions are associated with the use of SLT and areca nut (Singh et al., 2016). A few selected studies are described here to illustrate this determinant (Table 3.8).

A cross-sectional study conducted in adolescents in the USA reported a moderate level of knowledge about the undesirable effects of SLT, which had only little impact on male users (Lee et al., 1994). In another cross-sectional study in school students in the USA, significant differences were observed in the knowledge level and attitudes between SLT users and non-users; students with higher knowledge and attitude scores were less likely to use SLT (Goebel et al., 2000). In contrast, a study in a sample of university students in the USA reported no influence of the observed high knowledge level on the prevalence of SLT use, indicating a probable influence of multiple factors (Monson and Beaulieu, 2011). A school-based cross-sectional study in Pakistan conducted in adolescent users of areca nut and/or SLT reported that adolescents who had not attended the knowledge-based sessions on the harmful health effects of areca nut and/or SLT use were more likely to use these products (Hussain et al., 2017). In another study in adult chewers in Myanmar, use of areca nut was found to be significantly associated with low knowledge scores with respect to adverse health effects of areca nut use (Myint et al., 2016).

The level of knowledge about the harmful effects of areca nut or SLT use may also depend on the level of education, as reported in multiple studies, in which individuals with lower education levels had less awareness of the adverse effects of these substances (Khawaja et al., 2006; WHO Regional Office for South-East Asia, 2012; Myint et al., 2016; Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019).

Beliefs or perceptions about substances such as SLT or areca nut are another important factor determining their use. Some users believe that the use of SLT offers health benefits, such as improving sleep quality and relieving toothaches, headaches, and tiredness (Solhi et al., 2021). There is also a belief that SLT is less harmful than smoked tobacco (Singh et al., 2016). Certain perceived positive effects of chewing areca nut have been proven to be important determinants of its use; these include inducing relaxation, enhancing concentration and aiding decision-making, relieving boredom, improving stamina, curing cold, inducing a pleasant sensation, feeling energized, and conferring cosmetic benefits (Changrani et al., 2006; Banerjee et al., 2014; Myint et al., 2016; Lin et al., 2017; Hussain et al., 2018; Do and Vu, 2020).

(b) Social factors

(i) Sociodemographic determinants

Multiple studies in India have ascertained the role of age at initiation for SLT use; younger age at initiation is associated with a higher

Table 3.8 Determinants of use of smokeless tobacco and areca nut products

Determinants	Facilitators	Barriers	Country or territory	Reference
Individual factors				
Knowledge	Higher tendency to use SLT or AN if lower knowledge level about their harmful effects		India	Singh et al. (2016)
			Bangladesh	Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
			USA	Lee et al. (1994); Goebel et al. (2000)
			Myanmar	Myint et al. (2016)
			Pakistan	Hussain et al. (2017)
	Lower knowledge level about the harmful effects of SLT or AN was also due to low education level		Pakistan	Khawaja et al. (2006)
			Myanmar	Myint et al. (2016)
			Bangladesh	Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
			Indonesia	WHO Regional Office for South-East Asia (2012)
Perceptions	SLT use not as harmful as the other tobacco types (smoking) SLT perceived as suitable for dental health and treatment of dental pain		India	Singh et al. (2016); Shah et al. (2018)
			USA	Goebel et al. (2000)
		Belief that SLT causes one or more of the following: serious illnesses, serious illnesses in pregnancy, stroke, heart attack, oral cancer	Indonesia	WHO Regional Office for South-East Asia (2012)
			Bangladesh	Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
			India	TISS and MOHFW (2017)
		Belief that SLT use has undesirable effects, such as oral diseases or hypertension, chest pain or burning	USA	Lee et al. (1994); Goebel et al. (2000); Changrani et al. (2006); Monson and Beaulieu (2011)
	Perceived positive effects of AN chewing: considered cool in youth, as a cooling-off agent, improves work efficiency, improves stamina, relieves tension, cures cold, provides relaxation, relieves boredom, reduces stress, increases alertness, provides pleasant sensation, aids in digestion, prevents bad breath, reduces appetite, cosmetic benefits (red teeth as a sign of beauty).		Taiwan (China)	Lin et al. (2017); Yang and Lin (2017)
			USA (migrants)	Changrani et al. (2006); Banerjee et al. (2014)
			Pakistan	Rozi and Akhtar (2007); Hussain et al. (2017, 2018); Saqib et al. (2018)
			Sri Lanka	Lee et al. (2011); Sinha et al. (2012)
			India	Shah et al. (2018)
			Guam (USA)	Murphy and Herzog (2015)

Table 3.8 (continued)

Determinants	Facilitators	Barriers	Country or territory	Reference
Social factors				
1. Sociodemographic				
Age	Initiation of SLT and AN use at younger age		India	Singh et al. (2016); Sharapova et al. (2020)
			USA	
			Bangladesh	Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
	Continuation of AN and SLT use increases with age		Bangladesh	Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
			Cambodia	Sreeramareddy et al. (2014a)
			Indonesia	Lee et al. (2011)
			India	Rani et al. (2003); TISS and MOHFW (2017)
			Sri Lanka	Sinha et al. (2012)
			Thailand	WHO Regional Office for South-East Asia (2011)
			Nepal	Shrestha et al. (2019)
			Malaysia	IPH (2012)
			United Arab Emirates (migrants)	Ali et al. (2020)
			Uganda	Kabwama et al. (2016)
			United Kingdom (migrants)	Núñez-de la Mora et al. (2007)
			Pakistan	Hussain et al. (2017)

Table 3.8 (continued)

Determinants	Facilitators	Barriers	Country or territory	Reference
Sex	Higher prevalence of SLT use in males (reported that SLT includes all types of non-smoked tobacco products and AN)		Sri Lanka	Lee et al. (2011); Sinha et al. (2012)
			India	Sinha et al. (2012); TISS and MOHFW (2017)
			Pakistan	Hussain et al. (2017)
			Malaysia	IPH (2012)
	Higher prevalence of SLT use in females (reported that SLT includes all types of non-smoked tobacco products and AN, BQ)		Thailand	WHO Regional Office for South-East Asia (2011)
			Bangladesh	Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
	Higher prevalence of AN use in males		Myanmar	Myint et al. (2016)
			Sri Lanka	Lee et al. (2011)
			Nepal	Lee et al. (2011)
			Pakistan	Hussain et al. (2017)
			Taiwan (China)	Lee et al. (2011)
			China	Lee et al. (2011)
	Higher prevalence of AN (BQ) use in females		Malaysia	Lee et al. (2011)
			Indonesia	Lee et al. (2011)
Ethnicity	Higher initiation and continued use of SLT noted in White people		USA	Ebbert et al. (2006); Chaffee et al. (2018)

Table 3.8 (continued)

Determinants	Facilitators	Barriers	Country or territory	Reference
Residence	Higher prevalence of SLT use in rural areas than in urban areas		Indonesia	WHO Regional Office for South-East Asia (2012)
			India	MOHFW and IIPS (2019); Singh et al. (2020)
			Bangladesh	Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
			Thailand	WHO Regional Office for South-East Asia (2011)
			Malaysia	IPH (2012)
			WHO African Region	Kabwama et al. (2016); Bonnechère et al. (2019); WHO FCTC and ICMR-NICPR (2022)
			WHO Eastern Mediterranean Region	Al-Tayar et al. (2017); Alemi et al. (2021)
			Myanmar	Myint et al. (2016)
			Nepal	Shrestha et al. (2019)
2. Socioeconomic				
Income level	Higher prevalence of SLT use in poorer groups/ lowest-income groups/lowest-wealth-index groups		Cambodia	Sreeramareddy et al. (2014a)
			Bangladesh	WHO Country Office for Bangladesh (2018); Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
			India	Thakur et al. (2015); Bhan et al. (2016); Singh et al. (2016); Sinha et al. (2018a)
			Nepal	Shrestha et al. (2019)
Employment status	Higher prevalence of SLT use in unemployed people and homemakers		Indonesia	WHO Regional Office for South-East Asia (2012)
			India	Singh et al. (2016, 2020)

Table 3.8 (continued)

Determinants	Facilitators	Barriers	Country or territory	Reference
Type of occupation	Higher prevalence of AN use in taxi drivers, three-wheel taxi drivers, transportation workers, security guards, labourers, construction workers, agriculture workers, and plantation workers		Taiwan (China)	Yang and Lin (2017); Huang et al. (2020)
			Sri Lanka	Mahees et al. (2021)
			United Arab Emirates (migrants)	Ali et al. (2020)
	Higher prevalence of SLT use in military personnel (higher percentage of users serving as infantry and gun crew specialists, and enlisted personnel)		USA	Lin et al. (2018)
Education level	Higher prevalence of SLT and AN use with lower education levels Households with uneducated or less-educated members tend to consume more SLT		India	Palipudi et al. (2012); Singh et al. (2016); TISS and MOHFW (2017)
			Egypt	Palipudi et al. (2012)
			Philippines	Palipudi et al. (2012)
			Bangladesh	WHO Country Office for Bangladesh (2018); Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019)
			Nepal	Lee et al. (2011); Sreeramareddy et al. (2014a); Shrestha et al. (2019)
			Thailand	WHO Regional Office for South-East Asia (2011)
			Cambodia	Sreeramareddy et al. (2014a)
			Malaysia	Lee et al. (2011); IPH (2012)
			Taiwan (China)	Lee et al. (2011)
			Indonesia	Lee et al. (2011); WHO Regional Office for South-East Asia (2012)
			Sri Lanka	Lee et al. (2011)
			Myanmar	Myint et al. (2016)
			United Arab Emirates (migrants)	Ali et al. (2020)

Table 3.8 (continued)

Determinants	Facilitators	Barriers	Country or territory	Reference
3. Sociocultural				
Family or peer pressure	One of the main determinants for initiation of SLT or AN use		Pakistan	Rozi and Akhtar (2007); Hussain et al. (2017)
			Myanmar	Myint et al. (2016)
			Guam (USA)	Murphy et al. (2019)
	Considered rude and disrespectful to refuse chewing of AN (BQ) if family members or peers are chewing		Guam (USA)	Murphy and Herzog (2015); Murphy et al. (2019)
			Federated States of Micronesia	
			Pakistan	Hussain et al. (2017); Hussain et al. (2018)
Social reasons	During interactions with friends and peers and for social acceptability		Taiwan (China)	Lin et al. (2017)
			Guam (USA)	Murphy and Herzog (2015)
	Symbol of love and marriage		Taiwan (China)	Ma et al. (2017)
			India	Ahuja and Ahuja (2011)
	AN offered to visitors on special occasions		Sri Lanka	Wijesinghe (2018)
Cultural reasons	An acceptable alternative to smoking in Indian culture		India	Singh et al. (2016); Shah et al. (2018)
	Ancestral practice of the Kalunga community (the largest *quilombola* community in Brazil)		Brazil	Novais (2017)
Use of multiple substances	Strong association between current smoking practice and initiation of SLT use		USA	Ebbert et al. (2006)
	Concurrent AN (BQ) chewing in people who consume alcohol and/or smoke		Myanmar	Myint et al. (2016)
			Malaysia	Lee et al. (2011)
			Taiwan (China)	Lee et al. (2011); Lin et al. (2017); Yang and Lin (2017)
			United Arab Emirates (migrants)	Ali et al. (2020)
			Sri Lanka	Lee et al. (2011)

Table 3.8 (continued)

Determinants	Facilitators	Barriers	Country or territory	Reference
Environmental factors				
Easy availability	Around the house In neighbourhood stores From hawkers around educational institutions		Guam (USA) USA (migrants) India Pakistan	Murphy and Herzog (2015) Banerjee et al. (2014); Do and Vu (2020) Sinha et al. (2016) Hussain et al. (2017)
Family	Preparing the AN quid for elderly family members Strong influence from family members		Guam (USA) United Kingdom (migrants)	Murphy and Herzog (2015) Núñez-de la Mora et al. (2007)
School type	Higher tendency to use by students attending government schools than those attending private schools		Pakistan	Rozi and Akhtar (2007); Hussain et al. (2017)
Advertisements	Exposure to tobacco advertisements is a factor in SLT use, especially by young people Not seeing anti-tobacco advertisements		USA India Sudan Pakistan	Timberlake (2016) Arora et al. (2008) Almahdi et al. (2020) Rozi and Akhtar (2007)
Sports figures	SLT use by favourite professional baseball players (determinant for initiation and continuation of SLT use in youth)		USA	Chaffee et al. (2018)
Health messages	Lack of anti-AN and anti-SLT public health messages		USA (migrants)	Banerjee et al. (2014)

AN, areca nut; BQ, betel quid; SLT, smokeless tobacco; WHO, World Health Organization.
Compiled by the Working Group.

level of use and more prolonged use. In addition, the GATS-1 India documented that female individuals and people living in rural areas had a younger age at initiation (Singh et al., 2016). In Bangladesh, the GATS also documented a younger age at initiation of areca nut use in women (Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019). A study in middle school and high school students in the USA reported similar findings; male students initiated SLT use at a slightly older age compared with their female counterparts (Sharapova et al., 2020).

With regard to continuation of SLT or areca nut use, in a study in Pakistan conducted in adolescent users of areca nut (including betel quid) and/or SLT, age was positively associated with continued use (Hussain et al., 2017). In India, an increased likelihood of SLT use with increasing age was also observed; men aged ≥ 60 years were 4 times as likely and women aged ≥ 60 years were 8 times as likely to use SLT compared with younger individuals (aged 15–24 years) (Rani et al., 2003). The GATS-2 India further confirmed the increasing likelihood of SLT use with increasing age (TISS and MOHFW, 2017). This finding has also been noted in Afghanistan, Bangladesh, Malaysia, Nepal, and Thailand (WHO Regional Office for South-East Asia, 2011; IPH, 2012; Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019; Shrestha et al., 2019; Alemi et al., 2021). Another study in adolescent male SLT users in Pakistan reported a similar association; however, this weakened on multivariate analysis (Rozi and Akhtar, 2007).

With regard to sex, a higher prevalence of SLT use has been noted in male individuals in many countries, such as India, Malaysia, Pakistan, and Sri Lanka, whereas in Bangladesh and Thailand the reported prevalence of SLT use is higher in female individuals (Lee et al., 2011; WHO Regional Office for South-East Asia, 2011; IPH, 2012; Sinha et al., 2012; Hussain et al., 2017; TISS and MOHFW, 2017; Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019). Similarly, in a cross-sectional study in Myanmar men were 3 times as likely as women to chew areca nut (Myint et al., 2016). In Pakistan, men were also found to have a higher probability than women of initiating use of areca nut (including betel quid) (Hussain et al., 2017). Furthermore, a multicountry study also documented a higher prevalence of areca nut chewing in men than in women in China, Nepal, Sri Lanka, and Taiwan (China), whereas the opposite was observed in Indonesia and Malaysia (Lee et al., 2011).

Ethnicity was also reported to be a predictor of the initiation and continuation of SLT use; in the USA, a higher prevalence of initiation and continuation was found in White people than in individuals of other ethnicities (Ebbert et al., 2006; Chaffee et al., 2018).

Evidence from some countries in the WHO African Region and the WHO Eastern Mediterranean Region has shown a higher prevalence of SLT use in people living in rural areas (Al Tayar et al., 2017; Bonnechère et al., 2019; Alemi et al., 2021; WHO FCTC and ICMR-NICPR, 2022). In general, there are a higher percentage of adult SLT users in rural areas than in urban areas, especially in the countries in the WHO South-East Asia Region, such as Bangladesh, India, Myanmar, Nepal, and Thailand (WHO Regional Office for South-East Asia, 2011; Myint et al., 2016; Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019; MOHFW and IIPS, 2019; Shrestha et al., 2019). A recent report of the Global Youth Tobacco Survey (GYTS) India suggests a higher prevalence of SLT use in school-going adolescents in rural areas than in urban areas (MOHFW and IIPS, 2019; Table 3.8).

(ii) Socioeconomic determinants

The socioeconomic determinants of use of SLT and areca nut are income level, employment, and education level (Table 3.8).

A sufficient amount of literature is available on the role of these factors in India (Singh et al., 2016). A clear trend has been observed of higher prevalence of SLT use with lower income levels (Bhan et al., 2016). Thakur et al. (2015) showed that the probability of SLT use decreases with increasing income; wide economic inequalities in the patterns of SLT use were observed in all the states of India. The association between SLT use and low income levels was also observed in other countries in the WHO South-East Asia Region, such as Bangladesh, Cambodia, and Nepal (Sreeramareddy et al., 2014a; WHO Country Office for Bangladesh, 2018; Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019; Shrestha et al., 2019), and in countries in sub-Saharan Africa (Sreeramareddy et al., 2014b). An analysis of 140 countries by Sinha et al. (2018a) showed that, in general, the burden of SLT use is greatest in the lowest-income segments of the population.

Unemployment was found to be another predictor of increased likelihood of SLT use in India (Singh et al., 2020). Similarly, in Indonesia, the largest proportion of SLT users are homemakers (WHO Regional Office for South-East Asia, 2012). In contrast, it has also been reported that the expense incurred, especially for an unemployed person, is an important reason for quitting this practice (Murphy and Herzog, 2015). This may be due to the wide differential pricing of the various SLT products or even different brands of the same product (Nargis et al., 2014). Also, increases in the taxation of smoked tobacco products have led to comparatively lower prices of SLT.

The type of occupation may also determine the prevalence of use of SLT and areca nut. A high prevalence of SLT use has been reported in military personnel (especially in the infantry or gun crew specialists) in the USA (Lin et al., 2018). In Taiwan (China), drivers and construction workers were reported to have a higher prevalence of use of areca nut (including betel quid) (Huang et al., 2020). In Sri Lanka, three-wheel taxi drivers, transportation workers, security guards, construction workers, plantation workers, and fishers had a very high prevalence of use of commercially prepared SLT products (Mahees et al., 2021). It has been hypothesized that individuals in such occupations that require long working hours or continuously repeated activities benefit from the perceived positive effects of areca nut use, such as improving concentration, reducing hunger, inducing a sense of well-being, and relieving boredom (Winstock, 2002; Yang and Lin, 2017).

With regard to education level, the GATS-1 India reported clear educational gradients; individuals with no formal education or less than primary education were much more likely to be users of SLT or areca nut compared with individuals with secondary education or above (MOHFW and IIPS, 2010). This pattern persisted over time; the GATS-2 India reported that despite the decreasing trend in SLT use in all households, an association between lower education levels and higher prevalence of SLT use remained (TISS and MOHFW, 2017). A large multicountry study involving 13 low- and middle-income countries also reported high prevalence of tobacco use (including SLT) in individuals in the lower educational attainment category in Egypt and the Philippines, among other countries (Palipudi et al., 2012). The association between prevalence of SLT use and lower education levels was also observed in Bangladesh, Cambodia, Malaysia, Nepal, and Thailand (WHO Regional Office for South-East Asia, 2011; IPH, 2012; Sreeramareddy et al., 2014a; Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019). Similarly, the large Asian Betel-Quid Consortium study, which

involved 8922 chewers of areca nut (betel quid with or without tobacco), reported that individuals with higher education levels in Indonesia, Malaysia, Sri Lanka, and Taiwan (China) were less likely to be users of areca nut (Lee et al., 2011). The outcomes of another study, in adult chewers of areca nut in Myanmar, further corroborated these findings (Myint et al., 2016). However, individuals with higher education levels in Hunan (China) were slightly more likely to be users of areca nut, probably because of the influence of other factors (Lee et al., 2011).

(iii) Sociocultural determinants

Many studies have reported an association between various sociocultural factors and use of SLT and areca nut (Table 3.8).

Studies in Guam (USA), Myanmar, and Pakistan have documented that use of SLT and/or areca nut by family members and peer pressure are among the main determining factors for initiation of these practices (Rozi and Akhtar, 2007; Myint et al., 2016; Hussain et al., 2017; Murphy et al., 2019). The effect of peer pressure on SLT use was also reported in a review in India (Shah et al., 2018). Moreover, in a recent study in adolescent chewers in Pakistan, not chewing was considered rude if family members or friends were chewing (Hussain et al., 2018); this sentiment was shared by adults in Guam (USA) (Murphy et al., 2019).

The practice of areca nut chewing reinforces positive acceptance when socializing with friends in Taiwan (China), because sharing of areca nut is a usual practice during social gatherings (Lin et al., 2017; Ma et al., 2017). It is also considered a symbol of love and marriage in China, India, and Taiwan (China) (Ahuja and Ahuja, 2011; Ma et al., 2017). In Sri Lanka, areca nut is also offered to visitors on important occasions (Wijesinghe, 2018).

In India, tobacco smoking in the presence of elders is a social taboo, whereas wide social acceptance exists for tobacco chewing because it is deeply embedded in the Indian culture (Singh et al., 2016; Shah et al., 2018). The Kalunga community, the largest *quilombola* community in Brazil, still preserves ancestral practices such as the use of a type of snuff called *simonte* (Novais, 2017).

Current tobacco smoking was found to be a strong predictor of the initiation of SLT use (Ebbert et al., 2006). In addition, concurrent use of areca nut (including betel quid) was observed along with alcohol consumption and/or smoking in various settings (Lee et al., 2011; Myint et al., 2016; Lin et al., 2017; Yang and Lin, 2017; Ali et al., 2020).

(c) Environmental factors

Some of the adult participants in a pilot study conducted in Guam (USA) cited readily available areca nut, especially around the house, and the practice of preparing the areca nut by softening it orally to enable use by the toothless elders in the family as the main reasons for initiation of areca nut chewing (Murphy and Herzog, 2015).

Evidence from India and Pakistan has also shown that the easy availability of SLT and areca nut from hawkers around educational institutions, such as schools, plays a major role in facilitating their use in adolescents (Sinha et al., 2016; Hussain et al., 2017). The school environment may also play a role in determining use of SLT and areca nut. A study conducted in adolescent male high school students in Pakistan observed a higher prevalence of SLT use in students attending government schools than in those attending private schools (Rozi and Akhtar, 2007).

Exposure to advertisements for SLT and areca nut products is another determining factor for the use of these products. A cross-sectional study in 11 462 adolescent students in India reported that greater exposure to tobacco advertisements significantly increased the risk of initiating tobacco use; a dose–response effect was noted for a subset of students (Arora et al., 2008). In

addition, a study in male high school students in Pakistan found a significantly higher tendency to SLT use in those who did not see anti-tobacco advertisements (Rozi and Akhtar, 2007). In the Sudan, exposure to the advertisement of *toombak* at point of sale is associated with its increased perceived accessibility (Almahdi et al., 2020). Lack of anti-areca nut and anti-SLT public health messages was also cited as a facilitator of areca nut and SLT use by a group of South Asian immigrants in the USA (Banerjee et al., 2014). In the USA, perceived SLT use by favourite professional baseball players was shown to increase the susceptibility to initiation and continuation of SLT use in adolescent baseball players (Chaffee et al., 2018).

3.3 Interventions for cessation of use

The review included published intervention studies with intervention and control groups, such as randomized controlled trials (RCTs) and cohort studies. For those on behavioural interventions alone, studies with follow-up from the start of the intervention of ≥ 6 months were included, and for those on pharmacological interventions (alone or in combination with behavioural interventions), studies with follow-up of ≥ 6 weeks were included.

The review excluded studies such as those not targeted at SLT or areca nut use but at smoking cessation, those targeted at SLT or areca nut use but non-cessation studies, non-randomized intervention trials, and studies with SLT quit attempts, reduction, or withdrawal symptoms as the primary end-point.

When the RR and 95% CI for cessation of SLT use were not provided by the authors, they were calculated by the Working Group for each outcome with the longest follow-up period. In most studies assessing the effectiveness of pharmacological interventions alone or in combination with behavioural interventions, abstinence is defined by 7-day point-prevalence abstinence (short-term abstinence assessment) and prolonged or continuous abstinence (long-term abstinence assessment) confirmed by biochemical validation or self-reporting. Prolonged or continuous abstinence was defined as a preferred measure, and point prevalence was defined as a secondary measure recommended by Hughes et al. (2003).

3.3.1 Behavioural interventions

This section reviews studies assessing the effectiveness of behavioural interventions alone for cessation of SLT and/or areca nut use, both in adults and in youth.

(a) Behavioural interventions in adults

Nine studies (7 RCTs and 2 cohort studies) using behavioural interventions for SLT cessation were conducted in adults. Two of the largest studies were cohort studies conducted in India (Gupta et al., 1992; Anantha et al., 1995); most of the studies (6) were conducted in the USA (Stevens et al., 1995; Severson et al., 1998, 2007, 2008, 2009; Walsh et al., 1999), and one study was conducted in Sweden (Virtanen et al., 2015) (Table 3.9).

The earliest interventions took place in India. One quasi-experimental cohort trial was carried out for 10 years in Ernakulam District, Kerala, India, in 7033 users of betel quid with tobacco, to reduce the incidence of oral mucosal lesions by persuading participants to quit tobacco use. Interventions were carried out through house-to-house visits followed by an oral examination and an educational talk by a dentist and social scientist, along with relevant information, education, and communication materials such as films, radio broadcasts, posters, local newspaper articles, and lantern slides in local cinemas. [At 10 years of follow-up, a statistically significant effect was noted for the cessation intervention: relative risk (RR), 2.81; 95% confidence interval (CI), 2.38–3.32] (Gupta et al., 1992). The incidence

Table 3.9 Behavioural interventions for cessation of smokeless tobacco and/or areca nut use in adults

Reference Location	Study design Study population	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Gupta et al. (1992) Ernakulam District, Kerala, India	Cohort study (quasi-experimental) Men and women, aged ≥ 15 years Betel quid with tobacco[b] 10-year follow-up	4619 House-to-house survey/interview, oral examination, educational talk by dentist and social scientist, tailored films, radio broadcasts, posters, local newspaper articles, exhibition of lantern slides in local cinemas, dental camps	2414 Interview, oral examination, brief educational talk, advice to quit tobacco by dentist	At 120 months (10 years), quit rate: Men: I: 15.1% C: 2.3% Women: I: 18.4% C: 7.8% [RR (95% CI): Men: 6.52 (3.96–10.76) Women: 2.37 (1.98–2.83) Overall: 2.81 (2.38–3.32)]	Strengths: large sample size; long follow-up on cessation and OPMDs Limitations: ITT data absent; control group was not concurrent in time; not an RCT; results were not confirmed biochemically
Anantha et al. (1995) India	Cohort study (quasi-experimental) Men and women, all ages Chewed tobacco[a,b] 5-year follow-up	6714 Anti-tobacco education through handbills, folders, cards, a photo album, portable display boards, and audiovisual aids (films in local languages)	Two control areas: Control area 1: 12 152 Control area 2: 8171 No anti-tobacco education	At 60 months (5 years), quit rate in men: I: 30.2% Control area 1: 1.2% Control area 2: 1.1% [RR (95% CI): 25.70 (13.26–49.84)]	Strengths: long-term intervention; large sample size Limitations: age group of participants in intervention and control arms not mentioned; no randomization; quit rate in women not mentioned; ITT data absent; results were not confirmed biochemically RR was calculated by the Working Group comparing intervention with combination of both control arms and only for men
Stevens et al. (1995) USA	RCT Men, aged ≥ 15 years Moist snuff and chewing tobacco[a] 12-month follow-up	245 Oral examination, prophylactic treatment, patient education (with feedback), advice to quit SLT products by DH, follow-up by dentist, video and brief counselling session, brief self-help booklet, telephone number of a 24-hour advice line, a quit kit and follow-up call by DH after 1 week, tip sheets, monthly newsletters	273 Oral examination, brief advice to quit	At 12 months, quit rate: I: 18.4% C: 12.5% RR (95% CI): 1.47 (0.83–2.6)	Strength: long-term follow-up Limitations: this study was contaminated with NRT use by 4.5% in the intervention arm and 6.4% in the control arm; results were not confirmed biochemically RR calculated by Ebbert et al. (2015)

Table 3.9 (continued)

Reference Location	Study design Study population	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Severson et al. (1998) USA	RCT Men and women, aged ≥ 15 years SLT[a] 12-month follow-up	394 Oral examination, advice to quit SLT use, informative pamphlets, quit kit, setting of a quit date, motivational video, telephonic follow-up within 2 weeks	293 Advice to quit	At 12 months, quit rate: I: 10.2% C: 3.3% RR (95% CI): 3.03 (1.44–6.37)	Strength: long-term follow-up Limitation: results were not confirmed biochemically RR calculated by Ebbert et al. (2015)
Walsh et al. (1999) USA	RCT Men College baseball and football athletes SLT[a] 12-month follow-up	171 Oral examination by dentist, advice to quit tobacco use, self-help guide, brief counselling by DH (to SLT users, and also in groups to non-users), nicotine gum, telephone support	189 No intervention	At 12 months, quit rate: I: 35.1% C: 15.9% RR (95% CI): 2.21 (1.50–3.25)	Strength: long-term follow-up Limitations: nicotine gum was used by only 10% in the intervention group; no biochemical confirmation; 4% (7 in the intervention group and 5 in the control group) of the SLT users who were non-smokers at baseline started smoking cigarettes; of these athletes, only 1 in the intervention group quit SLT use Quit rates and RR calculated by Ebbert et al. (2015)
Severson et al. (2007) USA	RCT Men (majority) and women, aged 17–82 years SLT[a] 12-month follow-up	535 Assisted self-help: SLT quitting manual, video, telephone counselling	534 SLT quitting manual only	At 12 months, quit rate (based on ITT): I: 12.9% C: 9.7% RR (95% CI): 1.32 (0.94–1.86)	Strength: long-term follow-up Limitation: results were not confirmed biochemically RR calculated by Ebbert et al. (2015)
Severson et al. (2008) USA	RCT Men SLT[a] 6-month follow-up	1260 Enhanced website: guided, interactive programme to help each user create a tailored plan for quitting and relapse prevention, streaming video, broader range of printable useful resources, annotated links to external websites, two web forums, two modules (planning to quit and staying quit)	1263 Basic website: printable pocket guide and useful resources, links to external websites on SLT cessation and oral cancer	At 6 months, quit rate: [I: 21.4% C: 16.8% RR (95% CI): 1.28 (1.09–1.50)]	Limitation: results were not confirmed biochemically

Table 3.9 (continued)

Reference Location	Study design Study population	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Severson et al. (2009) USA	RCT Male military personnel SLT 6-month follow-up	392 SLT cessation manual, video cessation guide tailored to military personnel, telephone counselling	393 Advice to quit SLT use, referral to local military installation tobacco cessation programmes	At 6 months, quit rate: I: 30.3% C: 15.3% RR (95% CI): 1.98 (1.50–2.61)	Limitation: results were not confirmed biochemically Quit rates and RR calculated by Ebbert et al. (2015)
Virtanen et al. (2015) Sweden	RCT (FRITT study) Men and women, aged 18–75 years *Snus*[a] 6-month follow-up	225 94 SLT users Structured brief advice based on the 5A model[c]	242 100 SLT users Usual care	At 6 months, quit rate: I: 7.5% C: 2% RR (95% CI): 3.72 (0.79–17.47)	Limitations: number of SLT users in intervention and control groups was limited; large loss to follow-up; results were not confirmed biochemically Quit rates and RR calculated by Ebbert et al. (2015)

AN, areca nut; C, control; CI, confidence interval; DH, dental hygienist; FRITT, Free from Tobacco in Dentistry; I, intervention; ITT, intention-to-treat analysis; NRT, nicotine replacement therapy; OPMDs, oral potentially malignant disorders; RCT, randomized controlled trial; RR, relative risk; SLT, smokeless tobacco.

[a] SLT only.

[b] AN with tobacco.

[c] 5A model: (1) Asking about tobacco use, (2) Advising to quit, (3) Assessing willingness to quit, (4) Assisting the tobacco user in quitting, for instance by providing information on available counselling and medications, and (5) Arranging follow-up contacts.

rate of leukoplakia decreased significantly over the 10-year study period, and much more so in the intervention cohort than in the control cohort. [The results were based only on the response of participants and were not confirmed biochemically. RR with 95% CI and intention-to-treat analysis were not provided by the authors, and the control group was not concurrent in time.]

An anti-tobacco community education programme was conducted through trained health workers in Kolar District, Karnataka, India, in an intervention area (n = 6714) and two control areas (n = 12 152 in control area 1 and n = 8171 in control area 2) (Anantha et al., 1995). The intervention, which included anti-tobacco education through handbills, folders, cards, a photo album, portable display boards, and films in local languages, was provided only to the intervention group. After 5 years, the prevalence of tobacco chewing in men decreased significantly in the intervention group, from 16.8% to 8.1%, and remained almost unchanged in the control group (6.9% vs 7.1% in control area 1, and 11.4% vs 11.4% in control area 2) [RR, 25.70; 95% CI, 13.26–49.84]. [The age group of the participants was not mentioned. Results were not confirmed biochemically. RR with 95% CI and intention-to-treat analysis were not provided.]

More recently, the 7 RCTs conducted in the USA and Sweden assessed the impact of SLT cessation interventions. Most of these studies used one or more of the following behavioural interventions: brief advice to quit SLT use, a self-help booklet or cessation manual, tip sheets, monthly newsletter, pamphlets, and/or video and telephone calls for brief counselling and follow-up (Table 3.9). Of the 7 RCTs, 4 studies (Severson et al., 1998, 2008, 2009; Walsh et al., 1999) showed statistically significant effects and are described below.

Severson et al. (1998) conducted a brief dental office-based intervention in 687 SLT users (n = 394 in the intervention arm and n = 293 in the control arm) at 75 dental practices in Oregon (USA). For the participants in the intervention arm, an oral examination was conducted, followed by advice to quit SLT use and the setting of a quit date, informative pamphlets, a quit kit and a motivational video, and telephonic follow-up within 2 weeks. Participants in the control arm were provided with usual care and only advice to quit. At 12 months, the cessation rate of SLT use was 10.2% in the intervention group compared with 3.3% in the usual-care group (RR, 3.03; 95% CI, 1.44–6.37; Ebbert et al., 2015). [Results were not confirmed biochemically.]

Walsh et al. (1999) conducted an athletic team-based SLT cessation programme based on cognitive social learning theory in 360 male college baseball and football athletes. The intervention included an oral examination by a dentist, advice to quit SLT use, a self-help guide, individual or group counselling by a dental hygienist, telephone support, and nicotine gum in some participants. At 12 months, the cessation rate of SLT use was 35.1% in the intervention colleges and 15.9% in the control colleges (RR, 2.21; 95% CI, 1.50–3.25; Ebbert et al., 2015). [Results were not confirmed biochemically. Nicotine gum was used by 10% of participants at intervention colleges, and 4% of the SLT users who were non-smokers at baseline started smoking cigarettes.]

Severson et al. (2008) assessed the impact of an interactive, tailored web-based intervention (enhanced condition) versus a more linear, text-based website (basic condition) in 2523 adult SLT users in the USA. At 6 months of follow-up, the cessation rate of SLT use was 21.4% in the enhanced condition and 16.8% in the basic condition [RR, 1.28; 95% CI, 1.09–1.50]. [Results were not confirmed biochemically.]

An RCT was conducted in 785 male military personnel who used SLT, recruited from 24 military dental clinics across the USA during annual dental examinations (Severson et al., 2009). The behavioural intervention included an SLT cessation manual, a videotape cessation guide tailored

to military personnel, and three 15-minute telephone counselling sessions using motivational interviewing methods. The usual care provided to the controls consisted of standard procedures of the annual dental examination, including advice to quit SLT use and referral to local tobacco cessation programmes. At 6 months, the cessation rate of SLT use was 30.3% in the behavioural intervention arm and 15.3% in the usual-care arm (RR, 1.98; 95% CI, 1.5–2.61; Ebbert et al., 2015). [Results were not confirmed biochemically.]

A recent meta-analysis (Nethan et al., 2020) reported efficacy of behavioural interventions for SLT cessation in adults (RR, 1.63; 95% CI, 1.32–1.94) in both developed countries (RR, 1.39; 95% CI, 1.16–1.63) and developing countries (RR, 2.79; 95% CI, 2.32–3.25). Of the 16 studies included in the meta-analysis, 8 studies (Gupta et al., 1992; Stevens et al., 1995; Severson et al., 1998, 2007, 2008, 2009; Walsh et al., 1999; Virtanen et al., 2015) are summarized above.

In addition, in a study conducted in Minnesota (USA) among 210 adult male users of spit tobacco, group behavioural interventions alone provided a higher long-term abstinence rate than the use of nicotine gum with minimal contact (Hatsukami et al., 1996; for details, see Section 3.3.3).

(b) Behavioural interventions in youth

Interventions for cessation of SLT use in youth are different from those in adults, because the related health risks are not a major concern for this age group. A total of 5 studies (4 RCTs and 1 cohort study) were found that assessed behavioural interventions for SLT cessation in youth. The 4 RCTs were conducted in the USA in schools and colleges, in baseball and football players and other athletes (Gansky et al., 2002, 2005; Walsh et al., 2010; Danaher et al., 2013). The cohort study was conducted in India (Stigler et al., 2007) (Table 3.10).

Walsh et al. (2010) conducted an SLT cessation intervention study in 246 male baseball players aged 14–18 years in rural high schools in the USA who used SLT, and showed a significant effect at 12 months of follow-up. The intervention involved peer-led educational sessions, an oral examination, brief advice to quit SLT use, a self-help guide, a follow-up oral examination, and group cessation counselling sessions led by the school nurse. In SLT users who were non-smokers at baseline, at 12 months of follow-up the cessation rate of SLT use was 62% in the intervention arm and 36% in the control arm [RR, 1.70; 95% CI, 1.50–1.86]. [Results were not confirmed biochemically.] In this study, the male students who used SLT only were more likely to quit SLT use than those who also smoked (i.e. dual users).

Gansky et al. (2005) conducted a study in 637 collegiate baseball athletes aged 17–20 years who used spit tobacco at 52 colleges in California (USA). The participants in the intervention arm received oral cancer screening with feedback and brief counselling during the pre-season health screenings, support from a certified athletic trainer for SLT cessation, and a peer-led educational team meeting. The participants in the control arm received the usual anti-tobacco education, and the intervention materials were distributed only after the study ended. At 12 months, the cessation rate of SLT use in the intervention group (36%) was not significantly different from that in the control group (37%) (RR, 0.98; 95% CI, 0.80–1.20; Ebbert et al., 2015). In a larger cohort of 948 students from the same colleges, a significant positive effect of the intervention on the prevention of initiation of SLT use was observed (RR, 0.58; 95% CI, 0.35–0.99). [Results were not confirmed biochemically.]

Danaher et al. (2013) assessed a web-based intervention for SLT cessation, called the MyLastDip programme, in SLT users aged 14–25 years in the USA; 857 SLT users were randomly assigned to receive the enhanced website-based tailored intervention, and 859 SLT

Table 3.10 Behavioural interventions for cessation of smokeless tobacco and/or areca nut use in youth

Reference Location	Study design Study population	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Gansky et al. (2002) USA	RCT Males High school baseball athletes Spit tobacco[a] 24-month follow-up	355 141 users of spit tobacco Oral examination by dentist, brief counselling, peer-led component (video, graphic slides, group discussion)	375 166 users of spit tobacco No intervention	At 24 months, quit rate: I: 23% C: 13% RR (95% CI): 2.03 (0.89–4.60)	Strength: long-term follow-up Limitation: results were not confirmed biochemically RR calculated by Carr and Ebbert (2012) Initiation of SLT use: 27% in intervention group, 28% in control group (RR, 1.03; 95% CI, 0.75–1.41)
Gansky et al. (2005) USA	Cluster RCT Males, aged 17–20 years Collegiate baseball athletes Spit tobacco[a] 12-month follow-up	883 (27 colleges) 285 SLT users Dental component: oral cancer screening examination by dentist and/or DH, brief advice to quit SLT use, self-help guide tailored to baseball athletes, brief counselling by DH, follow-up by certified athletic trainer (group sessions), referral to tobacco-cessation counsellors on campus or in the community (for athletes wanting more intensive support and problem-solving) Peer-led component: videos (one tailored to baseball athletes), slide presentation, discussion	702 (25 colleges) 352 SLT users Usual anti-tobacco education offered at their colleges; all intervention materials were distributed at the end of the study	At 12 months, quit rate: I: 36% C: 37% RR (95% CI): 0.98 (0.80–1.20)	Strength: long-term follow-up Limitation: results were not confirmed biochemically RR calculated by Ebbert et al. (2015) Initiation of SLT use: 5.1% in intervention colleges, 8.4% in control colleges (RR, 0.58; 95% CI, 0.35–0.99) Of the SLT-only users at baseline, 4% reported at follow-up that they had stopped SLT use but had initiated smoking Of the dual users at baseline, 14% reported at follow-up that they had quit SLT use but continued to smoke
Stigler et al. (2007) India	Cohort study (Project MYTRI) Male and female students, aged 10–16 years School students in grade 6–9 Chewing tobacco[a,b] 12-month follow-up	4009 (16 schools) Classroom activities (curriculum), school posters, parent postcards, peer-led health activism	4360 (16 schools) Delayed intervention	At 12 months, quit rate: I: 1.1% C: 0.9% [RR (95% CI): 1.23 (0.88–1.72)]	Strength: long-term follow-up Limitation: results were not confirmed biochemically

Table 3.10 (continued)

Reference Location	Study design Study population	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Walsh et al. (2010) USA	Cluster RCT Males, aged 14–18 years Baseball players SLT[a] 12-month follow-up	2270 123 SLT users Peer-led educational session (video, slide presentation, discussion), oral examination with feedback, brief advice to quit SLT use, self-help guide, follow-up oral examination by nurse, nurse-led group cessation counselling sessions	2461 123 SLT users No intervention	At 12 months, quit rate in baseline non-smokers: I: 62% C: 36% [RR (95% CI): 1.70 (1.50–1.86)[c]]	Strength: long-term follow-up Limitations: results were not confirmed biochemically; confounded by smoking in some participants Prevalence of SLT initiation in baseline non-SLT users: Overall: 3% in intervention group, 3% in control group (OR, 0.78; 95% CI, 0.49–1.23) In baseline non-smokers: 2% in intervention group, 3% in control group (OR, 0.63; 95% CI, 0.36–1.13) In baseline smokers: 9% in intervention group, 7% in control group (OR, 0.88; 95% CI, 0.51–1.51) SLT-only users at baseline (i.e. baseline non-smokers) reported a significantly higher percentage of smoking at follow-up (19.4%)
Danaher et al. (2013) USA	RCT (MyLastDip programme) Males (majority) and females, aged 14–25 years SLT[a] 6-month follow-up	857 Enhanced condition: personalized best-practices SLT cessation programme with interactive and multimedia features, resource section with informational materials	859 Basic condition: online version of a self-help guide, resource section with informational materials, links to websites with content on SLT cessation and relaxation strategies	At 6 months, quit rate: I: 22.6% C: 21.9% RR (95% CI): 1.07 (0.87–1.31)	Limitation: results were not confirmed biochemically RR calculated by Ebbert et al. (2015)

AN, areca nut; C, control; CI, confidence interval; DH, dental hygienist; GEE, generalized estimating equation; I, intervention; MYTRI, Mobilizing Youth for Tobacco-Related Initiatives in India; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SLT, smokeless tobacco.

[a] SLT only.

[b] AN with tobacco.

[c] The calculation did not adjust for the fact that the OR reported by the authors comes from a GEE model that adjusted for clustering at schools.

users (controls) used the simple website, which provided guidelines in static text. At 6 months, in the intention-to-treat analysis, the cessation rate of SLT use was 22.6% in the intervention group and 21.9% in the control group (RR, 1.07; 95% CI, 0.87–1.31; Ebbert et al., 2015). [Results were not confirmed biochemically.]

A 2-year school-based, multicomponent tobacco intervention, called Project MYTRI: Mobilizing Youth for Tobacco-Related Initiatives in India, was conducted in two large cities (Delhi and Chennai) at 32 schools (16 schools in the intervention arm and 16 in the control arm) with two cohorts of students who were in grades 6 and 8, aged 10–16 years, when the study began (Stigler et al., 2007). Three surveys were conducted: the first at baseline in 2004, the second at the midpoint in 2005, and the third at the end of the intervention in 2006. The intervention was carried out by trained field staff, teachers, and peer leaders and consisted of four primary components: (i) behavioural, (ii) awareness generation with classroom activities and posters, (iii) parental involvement, and (iv) peer leadership in health activism. The controls received a delayed intervention. At 12 months, the cessation rate of SLT use was 1.1% in the intervention arm and 0.9% in the control arm [RR, 1.23; 95% CI, 0.88–1.72]. [Results were not confirmed biochemically, and RR with 95% CI and intention-to-treat analysis were not provided by the authors. The Working Group noted that in this study the term "SLT" may include products with SLT only and products with areca nut and tobacco, because both are predominant in India.]

In the recent meta-analysis by Nethan et al. (2020), behavioural interventions for SLT cessation did not prove effective in youth overall (RR, 1.07; 95% CI, 0.73–1.41), in developed countries (RR, 1.39; 95% CI, 0.58–2.21), or in developing countries (RR, 0.87; 95% CI, 0.68–1.07). Of the 3 studies included in the meta-analysis, 2 studies (Stigler et al., 2007; Walsh et al., 2010) are summarized above.

3.3.2 Pharmacological interventions

This section reviews studies assessing the effectiveness of pharmacological interventions alone for cessation of SLT or areca nut use. Nicotine replacement therapy, such as nicotine gums, lozenges, patches, and inhalers, and non-nicotine agents such as bupropion and varenicline are used as pharmacological interventions for tobacco cessation (Aubin et al., 2014). A total of 3 RCTs were considered; one was conducted in India (Raja et al., 2016), one in the USA (Severson et al., 2015), and one in Taiwan (China) (Hung et al., 2020) (Table 3.11).

(a) Nicotine replacement therapy

A worksite-based RCT in India evaluated and compared the effectiveness of nicotine gum (2 mg strength) and oral health education in 40 male users of SLT and areca nut (Raja et al., 2016). The tobacco abstinence rate (biochemically confirmed by cotinine levels in urine) at 3 months was higher in the nicotine gum group than in the group that received oral health education, but the difference was not statistically significant [RR, 1.33; 95% CI, 0.70–2.56]. [Limitations of this study are the small sample size, the short follow-up period, no mention of nicotine gum treatment period or frequency of gum intake, and the presence of one bidi smoker in the nicotine gum group.]

A web-based study (Severson et al., 2015), conducted in 1067 users of SLT in the USA, assessed the effectiveness of three separate interventions for SLT cessation: (a) nicotine lozenge (4 mg for 12 weeks) together with telephone counselling for 3 weeks (intervention arm), (b) nicotine lozenge (4 mg for 12 weeks) alone, and (c) telephone counselling only. In the study, groups (b) and (c) were considered as two control arms. [The Working Group assessed the results of the lozenge-only arm (b), taking the telephone counselling-only arm (c) as the control arm. There was no significant difference between the

Table 3.11 Pharmacological interventions for cessation of smokeless tobacco and/or areca nut use

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Nicotine replacement therapy					
Severson et al. (2015) USA	RCT Male (98%) users of SLT[a] only who were ready to quit Web-based 3-month and 6-month follow-up	(a) Nicotine lozenge (4 mg for 12 weeks) plus 3 coaching calls[d] (for 3 weeks) (n = 357) (b) Nicotine lozenge (4 mg for 12 weeks) (n = 356)	(c) 3 coaching calls[d] (for 3 weeks) (n = 354)	7-day repeated PP all-tobacco abstinence rate at 3-month and 6-month assessments (ITT) (self-reported): (a) 43.1% (b) 32.6% (c) 31.6% Lozenge alone (b) versus coaching calls alone (c): [RR (95% CI): 1.02 (0.87–1.19)]	Strength: large sample size (> 100 for each arm) Limitations: unstated allocation concealment; no biochemical validation test Note: In this study, the two groups (b) nicotine lozenge-only group and (c) telephone counselling-only group were considered as two control arms. Based on the abstinence rates, the Working Group could estimate the effectiveness of the lozenge-only intervention, by comparing (b) versus (c)
Raja et al. (2016) India	Parallel RCT Male users of *khaini*[a] and *paan masala*[c] Worksite-based 3-month follow-up	NRT group: nicotine gum (2 mg, depending on frequency of tobacco intake) (n = 20)	Oral health education group (n = 20)	Tobacco abstinence rate at 3 months (urinary cotinine): [I: 25% C: 15%] [RR (95% CI): 1.33 (0.70–2.56)]	Limitations: small sample size; no mention of NRT treatment period or frequency of gum intake; no information on mean age of study participants; 1 smoker (bidi) was included in the NRT group; loss to follow-up was treated as non-abstinent

Table 3.11 (continued)

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Non-nicotine replacement therapy					
Hung et al. (2020) Taiwan (China)	Double-blind RCT Male users of AN (e.g. BQ)[c] with cigarette smoking habits (except for 2 participants assigned to moclobemide group) Health-care setting-based	Escitalopram (SSRI, 10 mg/day for 8 weeks) (n = 38) Moclobemide (reversible MAOI, 150 mg/day for 8 weeks) (n = 36)	Placebo (identical-appearing) (n = 37)	Continuous abstinence rate (ITT) for ≥ 6 weeks after 8-week treatment (urinary arecoline): Escitalopram: 34.2% Moclobemide: 33.3% Placebo: 5.4% Escitalopram versus placebo: Adjusted proportion ratio: 6.3 (95% CI, 1.5–26.1) [RR (95% CI): 6.33 (1.53–26.14)] Moclobemide versus placebo: Adjusted proportion ratio: 6.8 (95% CI, 1.6–28.0) [RR (95% CI): 6.17 (1.48–25.64)]	Strength: this is a novel study of prescribing antidepressants for cessation of AN use Limitations: the outcomes were confounded by the cigarette smoking habits; an assignment of behavioural therapy group as a control arm is lacking

AN, areca nut; BQ, betel quid; CI, confidence interval; ITT, intention-to-treat analysis; MAOI, monoamine oxidase inhibitor; NRT, nicotine replacement therapy; PP, point prevalence; RCT, randomized controlled trial; RR, relative risk; SLT, smokeless tobacco; SSRI, selective serotonin reuptake inhibitor.

[a] SLT alone.

[b] AN with SLT.

[c] AN alone.

[d] Three planned proactive telephone counselling calls: 1 week after randomization for initial call, 2–3 days after the quit date, and 14–21 days after the second call.

two groups in the all-tobacco abstinence rate at the 3-month and 6-month assessments of self-reported 7-day repeated point prevalence (RR, 1.02; 95% CI, 0.87–1.19). The main strength of this study is the large sample size. Limitations of this study are unstated allocation concealment and no biochemical validation test.]

(b) Non-nicotine replacement therapy

In Taiwan (China), areca nut (including betel quid) products are consumed without tobacco (Lee et al., 2011). A double-blind RCT was conducted in 111 male users of areca nut and betel quid, to assess the effectiveness of the antidepressants escitalopram (a selective serotonin reuptake inhibitor; 10 mg/day for 8 weeks) and moclobemide (a reversible monoamine oxidase inhibitor; 150 mg/day for 8 weeks) in treating areca nut or betel quid use disorder or areca nut addiction (Lee et al., 2018; Hung et al., 2020). Follow-up was every 2 weeks for the 8-week trial. The primary outcome was cessation of areca nut chewing, which was defined as patients who had quit use of areca nut products continuously for ≥ 6 weeks. After 8 weeks of treatment, 34.2% of participants in the escitalopram group, 33.3% in the moclobemide group, and 5.4% in the placebo group quit use of areca nut products continuously for ≥ 6 weeks. The adjusted proportion ratio for areca nut chewing cessation (adjusted for age, education level, cigarette smoking, and the level of betel quid use disorder) was 6.3 (95% CI, 1.5–26.1) for escitalopram [RR, 6.33; 95% CI, 1.53–26.14] and 6.8 (95% CI, 1.6–28.0) for moclobemide [RR, 6.17; 95% CI, 1.48–25.64], compared with the placebo group. [This is an innovative study prescribing antidepressants for cessation of use of areca nut or betel quid, but it has limitations such as being confounded by cigarette smoking and lack of behavioural therapy in the control arm.]

3.3.3 Combined pharmacological and behavioural interventions

This section reviews studies assessing the effectiveness of pharmacological interventions in combination with behavioural interventions for cessation of SLT or areca nut use. In addition to the study selection criteria mentioned earlier, the review excluded studies on a pharmacological intervention alone and studies with no placebo or behavioural intervention in the control group.

A total of 16 RCTs were evaluated (Table 3.12), of which 2 were on nicotine gum (Boyle, 1992; Hatsukami et al., 1996), 4 on nicotine patch (Howard-Pitney et al., 1999; Hatsukami et al., 2000; Stotts et al., 2003; Ebbert et al., 2013), 4 on nicotine lozenge (Ebbert et al., 2009, 2010; Danaher et al., 2015; Severson et al., 2015), 3 on bupropion (Glover et al., 2002; Dale et al., 2002, 2007), and 3 on varenicline (Fagerström et al., 2010; Ebbert et al., 2011; Jain et al., 2014). Most of the studies were conducted in the USA (Boyle, 1992; Hatsukami et al., 1996, 2000; Howard-Pitney et al., 1999; Dale et al., 2002, 2007; Glover et al., 2002; Stotts et al., 2003; Ebbert et al., 2009, 2010, 2011, 2013; Danaher et al., 2015; Severson et al., 2015); one study was in Norway and Sweden (Fagerström et al., 2010), and one study was in India (Jain et al., 2014). One study was conducted specifically in adolescents aged 14–19 years (Stotts et al., 2003). [The Working Group noted that in all the studies the same behavioural intervention was given in both the intervention arm and the control arm, which may limit the evaluation of the combined effect of pharmacological and behavioural interventions compared with no intervention.]

(a) Nicotine replacement therapy

(i) Nicotine gum

Boyle (1992) conducted the first RCT for SLT cessation using nicotine replacement therapy in 100 users of moist snuff in the USA. The study investigated the effectiveness for SLT cessation

Table 3.12 Combined pharmacological and behavioural interventions for cessation of smokeless tobacco and/or areca nut use

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Nicotine replacement therapy: nicotine gum					
Boyle (1992) USA	RCT Male users of SLT* only Mass/social media-based *Moist snuff and chewing tobacco 6-week follow-up	Nicotine gum (2 mg, 12 pieces/day) for 6 weeks with group meeting and group social support for behavioural skills training (20–60 minutes/week) for 4 weeks (n = 50)	Placebo gum with group meeting and group social support for behavioural skills training (20–60 minutes/week) for 4 weeks (n = 50)	Continuous all-tobacco abstinence rate at 6 weeks (CO and tobacco alkaloids): Nicotine gum: 50% Placebo gum: 40% [RR (95% CI): 1.25 (0.81–1.94)]	Loss to follow-up was treated as non-abstinent Different validation tests were used at baseline and during follow-up Limitations: control arm also received the behavioural intervention; in biochemical validation tests at baseline, saliva cotinine levels were significantly higher in the active gum group; short follow-up
Hatsukami et al. (1996) USA	RCT Male users of SLT* only who were motivated to quit (not regular users of other forms of tobacco products) Mass/social media-based *Spit tobacco 12-month follow-up	(a) 2 mg of nicotine gum (at least 6 pieces/day initially, then decrease) with group behavioural therapy** for 8 weeks (n = 55) (c) 2 mg of nicotine gum with minimal contact*** for 8 weeks (n = 51) **Group behavioural therapy: 8 sessions (45–60 minutes each over 10 weeks) ***Minimal contact: 4 brief sessions by nurse, self-help booklet	(b) Placebo gum with group behavioural therapy** (n = 50) (d) Placebo gum with minimal contact*** (n = 54)	7-day PP SLT abstinence rate at 12-month follow-up (salivary cotinine): (a) 34.5% (b) 26% (c) 17.6% (d) 27.8% Nicotine gum (a) versus placebo gum (b) with group behavioural therapy: [RR (95% CI): 1.20 (0.83–1.74)] Nicotine gum (c) versus placebo gum (d) with minimal contact: [RR (95% CI): 0.72 (0.41–1.26)]	Loss to follow-up was treated as non-abstinent Limitations: control arms also received the behavioural interventions; not enough description of the approach of group allocation of participants, although it was mentioned that they were randomized

Table 3.12 (continued)

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Nicotine replacement therapy: nicotine patch					
Howard-Pitney et al. (1999) USA	Double-blind RCT Male users of SLT* only (98% non-smokers) who were motivated to quit Mass/social media-based *Chewing tobacco 6-month follow-up	15 mg nicotine patch for 6 weeks plus minimal-contact behavioural therapy** for 6 weeks (n = 206) **2 pharmacy visits (with trained pharmacist), 2 support calls (48 hours and 10 days after the quit date), self-help materials	Placebo patch plus minimal-contact behavioural therapy** for 6 weeks (n = 204)	7-day PP SLT abstinence rate at 6 months after treatment (salivary cotinine): Active patch: 38% Placebo patch: 34% [RR (95% CI): 1.09 (0.90–1.33)]	Loss to follow-up was treated as non-abstinent Strength: large sample size (≥ 100 in each arm) Limitations: control arm also received the behavioural intervention; high relapse rate in both groups; at the 6-month follow-up, the response rate was low (74%) and the distribution by group was not described
Hatsukami et al. (2000) USA	Double-blind RCT Male users of SLT* only who were ready to quit (not regular users of other forms of tobacco products) Mass/social media-based *Spit tobacco 62-week follow-up	(a) Active nicotine patch (including tapering period of 21 mg for 6 weeks, 14 mg for 2 weeks, and 7 mg for 2 weeks) plus mint snuff for 10 weeks (n = 100) (b) Active nicotine patch (including tapering period, same as group a) and no mint snuff for 10 weeks (n = 100) Individual brief behavioural interventions (10 minutes) with self-help manual were given for all groups at 8 visits	(c) Placebo patch plus mint snuff for 10 weeks (n = 101) (d) Placebo patch and no mint snuff for 10 weeks (n = 101)	Continuous all-tobacco abstinence rate at 62-week assessment (saliva cotinine): (a) 33% (b) 29% (c) 21% (d) 28% Active patch (b) versus placebo patch (d): [RR (95% CI): 1.03 (0.76–1.39)]	Loss to follow-up was treated as non-abstinent No evidence of the effect of mint snuff, and no interaction with nicotine patch (a versus b) Strength: large sample size (≥ 100 in each arm) Limitations: control arms also received the behavioural intervention; not enough description of the approach of group allocation of participants, although it was mentioned that they were randomized

Table 3.12 (continued)

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Stotts et al. (2003) USA	RCT Adolescent male users of SLT* only who were motivated to quit Youth-targeted (ages 14–19 years) *Spit tobacco (snuff and/or chewing tobacco) 12-month follow-up	(a) Nicotine patch with 50 minutes of behavioural intervention** for 6 weeks (n = 98) **Based on National Cancer Institute educational materials, and invited for a free oral screening	(b) Placebo patch with 50 minutes of behavioural intervention** for 6 weeks (n = 100) (c) Usual care: 5–10-minute counselling with follow-up telephone call 2 weeks later (n = 105)	7-day PP spit tobacco abstinence rate (ITT) at 12 months (salivary cotinine): (a) 17.3% (b) 25.0% (c) 11.4% Active patch (a) versus placebo (b): [RR (95% CI): 0.69 (0.40–1.20)] Active patch (a) versus usual care (c): [RR (95% CI): 1.52 (0.77–3.01)]	Limitations: high dropout rate in the control group as a result of knowing that they had no chance of receiving NRT; a few participants also smoked
Ebbert et al. (2013) USA	Phase II RCT Male heavy users of SLT only (aged 18–55 years) who use ≥ 3 cans or pouches per week and no other tobacco products Mass/social media-based 6-month follow-up	Nicotine patch (two 21 mg patches/day for 6 weeks and one 21 mg patch/day for 2 weeks) with behavioural intervention* (n = 25) *Individualized sessions (4 study visits during the medication phase) with self-help manual, minimum of 10 minutes, delivered by trained research staff	Identical-appearing placebo patch for 8 weeks with behavioural intervention* (n = 27)	Prolonged all-tobacco abstinence rate at 6 months (urinary anabasine): Nicotine patch: 32% Placebo patch: 19% [RR (95% CI): 1.41 (0.81–2.47)]	Loss to follow-up was treated as non-abstinent Limitations: control arm also received the behavioural intervention; the dropout rate was higher in the placebo group

Table 3.12 (continued)

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Nicotine replacement therapy: nicotine lozenge					
Ebbert et al. (2009) USA	RCT pilot study Adult (97% male) users of SLT* only who were ready to quit Mass/social media-based *Snuff 6-month follow-up	Nicotine lozenge (4 mg for 12 weeks) with brief behavioural counselling** at each visit (n = 136) **Including best-practice topics (10 minutes long, at week 2, 4, 6, and 12), tailored to participant quitting status	Placebo lozenge (for 12 weeks) with brief behavioural counselling** at each visit (n = 134)	Prolonged SLT abstinence rate at week 24 (no verification by urinary cotinine): Nicotine lozenge: 30.2% Placebo lozenge: 23.1% [RR (95% CI): 1.19 (0.93–1.52)]	Loss to follow-up was treated as non-abstinent Strength: large sample size (≥ 100 in each arm) Limitations: control arm also received the behavioural intervention; a higher percentage of the active group (18.3%) had biochemical disconfirmation of the self-reporting compared with the placebo group (5.1%) in week 12 (end of medication)
Ebbert et al. (2010) USA	RCT pilot study Adult (97% male) users of SLT* only who wanted to quit Mass/social media-based *Snuff 6-month follow-up	Nicotine lozenge (4 mg for 12 weeks) with assisted self-help intervention** (n = 30) **Assisted self-help by a self-help quitting guide, telephone support (5–15 minutes) by trained study assistants	Placebo lozenge (for 12 weeks) with assisted self-help intervention** (n = 30)	Prolonged SLT abstinence rate (self-reported) at 6 months: Nicotine lozenge: 27% Placebo lozenge: 38% [RR (95% CI): 0.79 (0.43–1.43)]	Loss to follow-up was treated as non-abstinent Limitations: control arm also received the behavioural intervention; small sample size; no biochemically confirmed abstinence; unstated randomization method
Danaher et al. (2015) USA	RCT Adult (98% male) users of SLT only who wanted to quit Web-based 6-month follow-up	Interactive web-based intervention* plus lozenge (4 mg) for 12 weeks (n = 205) *Automated email reminders encouraged engagement with the programme before and after the quit date (supportive emails sent 2 days, 1 week, and 2 weeks after the quit date)	Web-based intervention* only (n = 202)	7-day repeated PP SLT abstinence rate (ITT) at 6 months (self-reported) (primary outcome): Intervention arm: 45.9% Control arm: 39.1% [RR (95% CI): 1.15 (0.95–1.39)]	Strength: large sample size (≥ 100 in each arm) Limitations: no placebo lozenge was given to control arm; control arm also received the behavioural intervention; unstated allocation concealment; no biochemical validation test

Table 3.12 (continued)

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Severson et al. (2015) USA	RCT Adult (98% male) users of SLT only who were ready to quit Web-based 3-month and 6-month follow-up	(a) Nicotine lozenge (4 mg for 12 weeks) plus 3 coaching calls* (for 3 weeks) (n = 357) *3 planned proactive telephone counselling calls: 1 week after randomization for initial call, 2–3 days after the quit date, and 14–21 days after the second call	(b) Nicotine lozenge (4 mg for 12 weeks) (n = 356) (c) 3 coaching calls* (for 3 weeks) (n = 354)	7-day repeated PP all-tobacco abstinence rate at 3-month and 6-month assessments (ITT) (self-reported): (a) 43.1% (b) 32.6% (c) 31.6% (a) versus (b): [RR (95% CI): 1.24 (1.08–1.44)] (a) versus (c): [RR (95% CI): 1.27 (1.10–1.47)]	Strengths: large sample size (≥ 100 in each arm) Limitations: unstated allocation concealment; no biochemical validation test
Non-nicotine replacement therapy: bupropion SR					
Glover et al. (2002) USA	Double-blind RCT Male users of SLT* only who were motivated to quit (smokers excluded) Mass/social media-based *Moist snuff 12-week follow-up	Bupropion SR 150 mg (for 7 weeks: 150 mg once a day for 3 days, 150 mg twice a day for days 4–49) and brief counselling** (n = 35) **Trained clinician encouraged participants via telephone (3 days after the quit date and during the follow-up phase), nurse or qualified staff provided brief individual counselling (< 5 minutes) at each visit during the treatment phase	Placebo (for 7 weeks: 1 tablet once a day for 3 days, 1 tablet twice a day for days 4–49) and brief counselling** (n = 35)	7-day PP SLT abstinence rate at 12 weeks after treatment (CO, cotinine, and NicCheck): Intervention arm: 40% Control arm: 26% [RR (95% CI): 1.36 (0.86–2.15)]	Loss to follow-up was treated as non-abstinent Limitations: control arm also received the behavioural intervention; small sample size; short follow-up; no mention of dropout or loss to follow-up

Table 3.12 (continued)

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Dale et al. (2002) USA	Double-blind pilot RCT Male users of SLT* only who were interested in quitting Mass/social media-based *Snuff and/or chewing tobacco 6-month follow-up	Bupropion SR 150 mg (for 12 weeks: 150 mg once a day for 3 days, 150 mg twice a day from day 4 onwards) with behavioural intervention** (n = 34) **10-minute behavioural intervention at each study visit	Placebo (identical-appearing, same dosage schedule) for 12 weeks with behavioural intervention** (n = 34)	Continuous all-tobacco abstinence rate at 24 weeks (biochemically confirmed): Intervention arm: 12% Control arm: 12% [RR (95% CI): 1.00 (0.48–2.09)]	Loss to follow-up was treated as non-abstinent Limitations: control arm also received the behavioural intervention; small sample size; nearly half of the participants (31 of 68) withdrew or were lost to follow-up; unstated randomization and double-blinding method
Dale et al. (2007) USA	Multicentre double-blind RCT Male users of SLT* only who wanted to quit Mass/social media-based *Snuff and/or chewing tobacco 12-month follow-up	Bupropion 150 mg twice a day for 12 weeks plus behavioural intervention** (n = 113) **All participants received an oral examination by a periodontist and behavioural intervention with a manual during the treatment and follow-up phases	Placebo for 12 weeks plus behavioural intervention** (n = 112)	Continuous all-tobacco abstinence rate at week 52 (urinary cotinine): Intervention arm: 18.6% Control arm: 21.4% [RR (95% CI): 0.91 (0.65–1.29)]	Loss to follow-up was treated as non-abstinent Strengths: long follow-up; large sample size (≥ 100 in each arm) Limitation: control arm also received the behavioural intervention
Non-nicotine replacement therapy: varenicline					
Fagerström et al. (2010) Norway and Sweden	Multicentre, double-blind, placebo-controlled, parallel-group RCT Adult (90% male) users of SLT* only Mass/social media-based *Swedish *snus* 26-week follow-up	Varenicline 1 mg twice a day (titrated up during the first week) for 12 weeks with brief behavioural counselling* (n = 213) *Simple advice and helpful tips at the discretion of the investigator	Placebo for 12 weeks with brief behavioural counselling* (n = 218)	Continuous SLT abstinence rate at weeks 9–26 (salivary cotinine): Intervention arm: 45% Control arm: 34% RR (95% CI): 1.42 (1.08–1.79)	Loss to follow-up was treated as non-abstinent Strength: large sample size (≥ 100 in each arm) Limitation: control arm also received the behavioural intervention

Table 3.12 (continued)

Reference Location	Study design Study population Recruitment	Intervention arm	Control arm	Efficacy of intervention	Comments/interpretation
Ebbert et al. (2011) USA	Double-blind, placebo-controlled, phase II RCT Male users of SLT only Mass/social media-based 6-month follow-up	Varenicline (0.5 mg once a day for 3 days, then 0.5 mg twice a day for days 4–7, then 1.0 mg twice a day for a total of 12 weeks) with brief behavioural counselling** (*n* = 38) **Individualized programme containing 4 sessions of counselling (10 minutes long) with an intervention manual	Matching placebo with brief behavioural counselling** (*n* = 38)	Prolonged SLT abstinence rate at 6 months (urinary cotinine): Intervention arm: 44.7% Control arm: 31.6% [RR (95% CI): 1.31 (0.84–2.04)]	Loss to follow-up was treated as non-abstinent Limitations: control arm also received the behavioural intervention; small sample size
Jain et al. (2014) India	Double-blind RCT Adult (97% male) SLT users (specific products used not mentioned) Population/community based 12-week follow-up	Varenicline (1 mg twice a day for 12 weeks) with behavioural counselling* (*n* = 119) *6-session counselling with manual-based intervention	Matching placebo with behavioural counselling* (*n* = 118)	7-day PP SLT abstinence rate at 12 weeks (urinary cotinine and CO) (ITT): Intervention arm: 25.2% Control arm: 19.5% [RR (95% CI): 1.18 (0.89–1.56)]	Strength: large sample size (≥ 100 in each arm) Limitations: no mention of the type of SLT products and whether they were with or without areca nut; the study did not observe a long-term effect of the treatment; adherence to varenicline use was low; unstated randomization and double-blinding method; control arm also received the behavioural intervention

CI, confidence interval; CO, carbon monoxide; ITT, intention-to-treat analysis; NRT, nicotine replacement therapy; PP, point prevalence; RCT, randomized controlled trial; RR, relative risk; SLT, smokeless tobacco; SR, sustained release.

of nicotine gum prescribed for 6 weeks along with behavioural support in the form of 4 weekly group meetings and group social support (Boyle, 1992). At the end of the 6-week study, there was no significant difference between the nicotine gum arm and the placebo arm in the continuous abstinence rate (verified by carbon monoxide and tobacco alkaloid metabolites analysis) for use of any tobacco (including SLT) [RR, 1.25; 95% CI, 0.81–1.94]. [Limitations of this study are the short follow-up period and that levels of salivary cotinine were significantly higher at baseline in the active nicotine gum group.]

In a study conducted in Minnesota (USA), 210 adult male users of spit tobacco were randomized to determine the effectiveness of nicotine gum and behavioural therapy (Hatsukami et al.,1996). The participants were randomly assigned to the following groups: (a) group behavioural therapy and nicotine gum, (b) group behavioural therapy and placebo gum, (c) minimal contact and nicotine gum, or (d) minimal contact and placebo gum. At 12 months, there were no significant differences in 7-day point-prevalence SLT abstinence rates between group a and group b [RR, 1.20; 95% CI, 0.83–1.74] or between group c and group d [RR, 0.72; 95% CI, 0.41–1.26]. [A limitation of this study is not enough description of the approach of group allocation of participants, although it was mentioned that they were randomized.]

In a systematic review of interventions for SLT cessation (Ebbert et al., 2015), based on these two trials (Boyle et al., 1992; Hatsukami et al., 1996), nicotine gum use did not increase abstinence compared with placebo (RR, 0.99; 95% CI, 0.68–1.43).

(ii) Nicotine patch

In a large double-blind RCT (Howard-Pitney et al., 1999), 410 adult users of chewing tobacco (SLT) (99% men) received either a nicotine patch (15 mg) or a placebo patch treatment for 6 weeks combined with minimal-contact behavioural intervention. At 6 months after the treatment, the biochemically confirmed 7-day point-prevalence SLT abstinence rate was slightly higher in the nicotine patch group than in the placebo patch group, but the difference was not statistically significant [RR, 1.09; 95% CI, 0.90–1.33]. [A limitation of this study is that at the 6-month follow-up, the response rate was low and the distribution by group was not described.]

In another large trial, conducted in Minnesota (USA) (Hatsukami et al., 2000), 402 adult participants (99% men) were randomly assigned to the following treatment groups for 10 weeks: (a) nicotine patch plus mint snuff, (b) nicotine patch and no mint snuff, (c) placebo patch plus mint snuff, or (d) placebo patch and no mint snuff. The participants were also given a self-help manual, and individual brief behavioural interventions were conducted (10 minutes) at 8 visits. At the 62-week assessment (12 months after treatment), the continuous abstinence rate was higher in the nicotine patch group (b) than in the placebo patch group (d), but the difference was not statistically significant [RR, 1.03; 95% CI, 0.76–1.39]. [A limitation of this study is not enough description of the approach of group allocation of participants, although it was mentioned that they were randomized.]

An RCT was conducted in adolescent male users of SLT in the USA to test the efficacy of nicotine patches in combination with behavioural intervention compared with the usual care (Stotts et al., 2003). About 303 participants (aged 14–19 years) were recruited from 41 high schools in Arkansas. Participants were provided with either a nicotine patch (group a) or a placebo patch (group b) for 6 weeks along with a behavioural intervention and were also invited for a free oral screening, or were provided usual care (group c). At the 1-year follow-up, no significant difference was noted between the nicotine patch group and the placebo patch group [RR, 0.69; 95% CI, 0.40–1.20] or between the nicotine patch group and the usual-care group [RR, 1.52;

95% CI, 0.77–3.01]. [A limitation of this study is a high dropout rate in the control group as a result of knowing that they had no chance of receiving nicotine replacement therapy; a few participants also smoked. The study was conducted in adolescents.]

Ebbert et al. (2013) conducted a phase II RCT in adult male heavy users of SLT (who used ≥ 3 cans or pouches per week). The intervention consisted of a 42 mg/day nicotine patch (for 6 weeks) followed by a 21 mg/day nicotine patch (for 2 weeks) along with behavioural counselling for SLT cessation. At 6 months, the continuous all-tobacco abstinence rate was higher in the nicotine patch group than in the placebo patch group, but the difference was not statistically significant [RR, 1.41; 95% CI, 0.81–2.47]. [A limitation of this study is that the dropout rate was higher in the placebo group. The low power of the test may be due to the small sample size.]

The systematic review by Ebbert et al. (2015) also did not report significantly increased abstinence with nicotine patch use (5 trials; RR, 1.13; 95% CI, 0.93–1.37). Of the 5 trials included in the systematic review, 4 trials (Howard-Pitney et al., 1999; Hatsukami et al., 2000; Stotts et al., 2003; Ebbert et al., 2013) are summarized above.

(iii) Nicotine lozenge

Two randomized pilot studies were conducted in adult (mostly male) snuff users to assess the effect of nicotine lozenge use (for 12 weeks) on SLT cessation (Ebbert et al., 2009, 2010; Table 3.12). Participants were randomly allocated to either a nicotine lozenge group or a placebo lozenge group, combined with behavioural intervention (i.e. brief behavioural counselling) (Ebbert et al., 2009) or a self-help quitting guide and telephone support (Ebbert et al., 2010). At 6 months, neither of the studies showed significant differences in prolonged SLT abstinence rates: [RR, 1.19; 95% CI, 0.93–1.52] (Ebbert et al., 2009) and [RR, 0.79; 95% CI, 0.43–1.43] (Ebbert et al., 2010).

A large, web-based intervention (the MyLastDip programme) was conducted in 407 adult (98% male) SLT users in the USA to evaluate the benefits of the website and nicotine lozenge (for 12 weeks) on SLT cessation (Danaher et al., 2015; Table 3.12). At 6 months, the 7-day repeated point-prevalence SLT abstinence rate for the website plus lozenge group was not significantly higher than that for the website-only group [RR, 1.15; 95% CI, 0.95–1.39]. [Limitations of this study are that no placebo lozenge was given to the control arm, unstated allocation concealment, and no biochemical validation test.]

Severson et al. (2015) conducted a large RCT in the USA using nicotine lozenge plus telephone counselling for SLT cessation in 1067 adult (98% male) participants recruited through an online marketing campaign. Participants were allocated to one of three groups: (a) nicotine lozenge (4 mg for 12 weeks) plus coaching calls (telephone counselling), (b) nicotine lozenge (4 mg for 12 weeks) alone, or (c) coaching calls alone. For the telephone counselling, three planned proactive calls were made: 1 week after randomization for the initial call, 2–3 days after the quit date, and 14–21 days after the second call. At the 3-month and 6-month assessments, the 7-day repeated point-prevalence all-tobacco abstinence rate was higher for nicotine lozenge plus coaching calls (43.1%) than for nicotine lozenge alone (32.6%) or coaching calls alone (31.6%). The differences were statistically significant for lozenge plus coaching calls versus lozenge only [RR, 1.24; 95% CI, 1.08–1.44] and for lozenge plus coaching calls versus coaching calls only [1.27; 95% CI, 1.10–1.47]. Overall, the all-tobacco abstinence rates were relatively high in all three groups. [A strength of this study is the large sample size. Limitations are unstated allocation concealment and no biochemical validation test.]

In the meta-analysis by Ebbert et al. (2015), nicotine lozenge intervention was effective in helping people quit SLT use (5 trials; RR, 1.36; 95% CI, 1.17–1.59), but the quality of the evidence

was rated as low. Of the 5 studies included in the systematic review, 4 trials (Ebbert et al., 2009, 2010; Danaher et al., 2015; Severson et al., 2015) are summarized above.

(b) Non-nicotine replacement therapy

(i) Bupropion

Bupropion is a monocyclic antidepressant that acts as a norepinephrine and dopamine reuptake inhibitor (Cooper et al., 1980). Sustained-release bupropion has been used to treat nicotine dependence and for cessation in cigarette smokers (Hurt et al., 1997; Jorenby et al., 1999; Cahill et al., 2013).

A double-blind RCT was conducted in 70 adult male users of moist snuff in the USA, using sustained-release bupropion (150–300 mg/day for 7 weeks) or placebo, combined with brief counselling (< 5 minutes) (Glover et al., 2002). At 12 weeks, the 7-day point-prevalence SLT abstinence rate was higher in the sustained-release bupropion plus brief counselling group than in the placebo plus brief counselling group, but the difference was not statistically significant [RR, 1.36; 95% CI, 0.86–2.15]. [Limitations of this study are the small sample size and no mention of dropout or loss to follow-up rates.]

A double-blind pilot RCT (Dale et al., 2002) and a double-blind multicentre RCT (Dale et al., 2007) were conducted in adult male SLT users in the USA to assess the effectiveness of bupropion 150 mg or placebo along with behavioural intervention over a period of 12 weeks, with long-term follow-up (at 6 months and 12 months, respectively). Neither of the studies found significant differences in the continuous all-tobacco abstinence rates between the two groups. [A strength of the Dale et al. (2007) study is the large sample size.]

In the meta-analysis by Ebbert et al. (2015), based on two trials, bupropion did not show a benefit in SLT cessation (RR, 0.89; 95% CI, 0.54–1.44). Both of these trials (Dale et al., 2002, 2007) are summarized above.

(ii) Varenicline

Varenicline, a partial agonist of the α4β2 nicotinic receptor (Coe et al., 2005), has been used for smoking cessation (Gonzales et al., 2006; Jorenby et al., 2006; Wu et al., 2006; Cahill et al., 2012). Varenicline inhibits the activation of dopaminergic activity caused by smoking while providing relief from the craving and withdrawal symptoms associated with smoking cessation attempts (Coe et al., 2005).

A large, multicentre, double-blind, placebo-controlled, parallel-group RCT was conducted in Norway and Sweden to evaluate the efficacy of varenicline for cessation of SLT (Swedish *snus*) use in 431 adult (mostly male) users (Fagerström et al., 2010). Participants were recruited through newspaper advertisements and were given either varenicline (1 mg) twice daily (titrated during the first week) with brief behavioural counselling, or placebo with brief behavioural counselling, for 12 weeks with follow-up to 14 weeks after treatment. All participants received brief advice and helpful tips at the discretion of the investigator, together with discussion of any topics or concerns they raised. The continuous SLT abstinence rate at weeks 9–26 was significantly higher in the varenicline plus behavioural counselling group than in the placebo plus behavioural counselling group (RR, 1.42; 95% CI, 1.08–1.79). [A strength of this study is the large sample size.]

Another double-blind, placebo-controlled, phase II RCT was conducted in the USA, using varenicline (for 12 weeks) with brief behavioural counselling for the treatment of SLT use (Ebbert et al., 2011). At 6 months, the prolonged SLT abstinence rate was not significantly higher in the varenicline plus behavioural counselling group than in the placebo plus behavioural counselling group [RR, 1.31; 95% CI, 0.84–2.04]. [A limitation of this study is the small sample size.]

Another large double-blind RCT was conducted in 237 adult (mostly male) users of SLT in India, using varenicline (1 mg twice per day for 12 weeks) with behavioural counselling as the intervention (Jain et al., 2014). The end-of-treatment 7-day point-prevalence SLT abstinence rate was higher in the varenicline group than in the placebo group, but the difference was not statistically significant [RR, 1.18; 95% CI, 0.89–1.56]. [A strength of this study is the large sample size. Limitations are that there was no mention of the type of SLT products and whether they were with or without areca nut, that the study did not observe a long-term effect of the treatment, and that adherence to varenicline use was low.]

In the meta-analysis by Ebbert et al. (2015), pooled results from two trials of varenicline reported a benefit in SLT cessation (RR, 1.34; 95% CI, 1.08–1.68). Both of these trials (Fagerström et al., 2010; Ebbert et al., 2011) are summarized above.

3.4 Policies and their impacts

3.4.1 Control policies for smokeless tobacco

(a) Introduction

The burden and the health effects of SLT use have shown that it poses a global public health challenge, like tobacco smoking (NCI and CDC, 2014). The WHO Framework Convention on Tobacco Control (FCTC) aims to reduce consumption of all forms of tobacco (as stated in Article 4.4) (WHO, 2003). The sixth session of the Conference of the Parties to the WHO FCTC reviewed the challenges related to SLT products and recommended that the countries apply relevant policy interventions for SLT products with the same rigour as those for smoked tobacco products (WHO FCTC, 2014).

However, it is difficult to have globally uniform regulations and guidelines pertaining to SLT products, because of the wide variations in the use, type of products, tobacco markets, and distribution patterns in different geographical regions. Other factors that make SLT control challenging include manufacturing, storage, and consumption patterns, inadequate regulatory processes, and illegal trade routes, but SLT control is an indispensable component of tobacco control efforts (Sinha et al., 2018b).

The WHO FCTC has been acceded to by 182 Parties as of May 2020 (WHO FCTC, 2021), and progress in its implementation is at an early intermediate stage for SLT (WHO, 2008). Table 3.13 gives the number of countries in which the individual policies have been implemented for SLT control (Mehrotra et al., 2019; WHO, 2021b).

The WHO MPOWER package for tobacco control (WHO, 2008) includes six evidence-based measures: monitoring tobacco use and prevention policies (M); protecting people from tobacco smoke (P); offering help to quit tobacco use (O); warning people about the harms of tobacco (W); enforcing bans on tobacco advertising, promotion, and sponsorship (E); and raising taxes on tobacco (R). Two thirds of the countries monitor SLT use. Just less than half of the countries offer help to quit SLT use, and more than one third have a quitline. Most countries have required the placement of pictorial health warnings on SLT packages, but many of these are small relative to the package size. At least half of the countries enforce bans on advertising and promotion of SLT products. Very few countries have provided data on raising taxes on SLT (Mehrotra et al., 2019; WHO, 2021b).

This section presents studies on the impact of the above-mentioned policies in terms of reduction in prevalence of SLT use, increased cessation of SLT use, thinking about quitting SLT use, reduction in frequency of SLT use, decrease in initiation of SLT use, or decrease in sales of SLT to youth, mainly as reported in successive national surveys (after 2011) for countries with a medium to high prevalence of SLT use (i.e. Bangladesh, India, the Sudan, Thailand, and the USA), or from a few other resources. The

Table 3.13 Tobacco control policies applicable to smokeless tobacco, and number of countries where they have been implemented

WHO FCTC policies applicable to SLT	Specific policy	Data year	Number of countries (%)[a]	Reference
Article 6: Price and tax measures on SLT	Data on price and taxation of SLT products	2018	34 (19%)	Mehrotra et al. (2019)
	Two-point data on SLT taxation	2018	11 (6%)	Mehrotra et al. (2019)
	Data on price elasticity and affordability of SLT	2018	2 (1%)	Mehrotra et al. (2019)
Article 9: Regulation of contents of SLT products Article 10: Regulation of disclosures of contents of SLT product	Ban on the display of quantitative information on relevant constituents or emissions of SLT	2021	43 (22%)	WHO (2021b)
	Mandate the display of qualitative information on relevant constituents or emissions of SLT	2021	26 (13%)	WHO (2021b)
	Data on pH and free nicotine in different SLT tobacco products	2018	6 (3%)	Mehrotra et al. (2019)
Article 11: Packaging and labelling of SLT products	Pictorial health warnings on SLT products	2020	47 (24%)	WHO (2021b)
	Pictorial health warnings ≥ 50% of package size	2020	41 (21%)	WHO (2021b)
	Text warnings ≥ 50% of package size	2020	23 (12%)	WHO (2021b)
Article 12: Education, communication, training, and public awareness on SLT	Anti-tobacco mass media campaign	2018	65 (36%)	Mehrotra et al. (2019)
	Data on adults who believe that using SLT causes serious illness	2018	19 (11%)	Mehrotra et al. (2019)
	Data on adults who noticed information about the dangers of using SLT	2018	1 (1%)	Mehrotra et al. (2019)
	Data on SLT users who noticed health warnings on SLT packages	2018	1 (1%)	Mehrotra et al. (2019)
	Tobacco use prevention is included in the school curriculum	2018	30 (17%)	Mehrotra et al. (2019)
	Training to prevent tobacco use in young people	2018	30 (17%)	Mehrotra et al. (2019)
	Non-classroom programmes or activities to teach tobacco use prevention to students	2018	29 (16%)	Mehrotra et al. (2019)
	Access to teaching and learning materials about preventing tobacco use in young people	2018	28 (16%)	Mehrotra et al. (2019)
Article 13: Ban on SLT advertising, promotion, and sponsorship (TAPS)	Ban on promotion on national television and radio	2020	166 (85%)	WHO (2021b)
	Ban on promotion in local magazines and newspapers	2020	155 (80%)	WHO (2021b)
	Ban on billboard and outdoor advertising	2020	158 (81%)	WHO (2021b)
	Ban on advertising at point of sale	2020	111 (57%)	WHO (2021b)
	Ban on free distribution in mail or through other means	2020	134 (69%)	WHO (2021b)
	Ban on promotional discounts	2020	126 (65%)	WHO (2021b)
	Ban on tobacco brands (product placement) on television or in films	2020	130 (67%)	WHO (2021b)
	Ban on tobacco products on television or in films	2020	49 (25%)	WHO (2021b)
	Complete ban on sponsorship	2020	66 (34%)	WHO (2021b)
	Fines for violations of bans on promotion and sponsorship	2020	151 (77%)	WHO (2021b)

Table 3.13 (continued)

WHO FCTC policies applicable to SLT	Specific policy	Data year	Number of countries (%)[a]	Reference
Article 14: Demand reduction measures concerning SLT dependence and cessation	Quitline available	2020	72 (37%)	WHO (2021b)
	Nicotine replacement therapy available	2020	117 (60%)	WHO (2021b)
	Nicotine replacement therapy available as essential medicine	2020	47 (24%)	WHO (2021b)
	Nicotine replacement therapy available (cost covered)	2020	57 (29%)	WHO (2021b)
	Cessation support available in health facilities and/or in hospitals	2020	125 (64%)	WHO (2021b)
	Cessation support available in offices of health professionals	2020	78 (40%)	WHO (2021b)
	Cessation support available in the community	2020	80 (41%)	WHO (2021b)
Article 16: Access to and availability of SLT to minors	Warning signboards at point of sale	2018	75 (42%)	Mehrotra et al. (2019)
	Ban on display of tobacco products at point of sale	2020	50 (26%)	WHO (2021b)
	Ban on tobacco products in the form of sweets, toys, candies, etc.	2020	103 (52%)	WHO (2021b)
	Prohibition of vending machines that contain tobacco products	2020	113 (58%)	WHO (2021b)
	Ban on free distribution of tobacco products to minors	2018	72 (40%)	Mehrotra et al. (2019)
	Ban on sale of loose SLT products	2018	18 (10%)	Mehrotra et al. (2019)
	Penalty against sellers for violations	2018	113 (63%)	Mehrotra et al. (2019)
Article 20: Research, surveillance, and exchange of information on SLT	Data on SLT use in adults	2020	125 (64%)	WHO (2021b)
	Data on recent SLT use in adults	2018	55 (31%)	Mehrotra et al. (2019)
	Data on SLT use in adolescents	2020	117 (60%)	WHO (2021b)
	Data on recent SLT use in adolescents	2018	70 (39%)	Mehrotra et al. (2019)
	Prevalence of SLT use > 10% in adults	2020	14 (7%)	WHO (2021b)
	Prevalence of SLT use > 10% in adolescents	2020	16 (8%)	WHO (2021b)
	Data on SLT-attributable major diseases risk factors	2018	10 (6%)	Mehrotra et al. (2019)

SLT, smokeless tobacco; WHO FCTC, World Health Organization Framework Convention on Tobacco Control.

[a] 180 countries for Mehrotra et al. (2019); 195 countries for WHO (2021b).

studies are described in the order of relevance to the WHO FCTC articles for which considerable progress has been shown (Articles 4–6, 11–14, 16, and 20, and bans on SLT products).

(b) Articles 4 and 5: Prevention of initiation of smokeless tobacco use in youth

The Global School Personnel Survey (GSPS) conducted in 2000 in the state of Bihar in India reported that nearly 78% of school personnel, including teachers, used tobacco (Sinha et al., 2002; Sorensen et al., 2005).

In the GYTS conducted in students in grades 8, 9, and 10 (generally aged 13–15 years) in 50 state government schools and 50 federal (central government) schools in Bihar, a significantly higher prevalence of ever and current tobacco use (for both smoking and SLT use) was found in students in state government schools without tobacco-free policies than in students in federal schools with tobacco-free policies. Classroom teaching about the harmfulness of tobacco use to health was also much more common in federal schools. Students in state schools were much more likely to have friends who used tobacco compared with students in federal schools (Sinha et al., 2004a). When the school personnel were surveyed (Sinha et al., 2004b), a significantly higher prevalence of smoking and SLT use was found in state schools than in federal schools. More than half of the personnel in the federal schools knew about the policy prohibiting tobacco use by personnel and students and about the means of enforcement. Teaching about the health consequences of tobacco use was carried out to some extent in the federal schools but not in the state schools, and the federal schools had some access to teaching materials on this topic. More than 90% of all personnel in both types of schools supported a policy prohibiting tobacco use in schools.

An RCT was conducted in teachers and staff of grades 8–10 in 72 state government schools in Bihar, in 2009–2010 and 2010–2011, to inform teachers of the dangers of tobacco use, to assist them to quit tobacco use (Sorensen et al., 2013), and to assess the implementation of the tobacco control polices (Mathur et al., 2016). The intervention, called the Tobacco-Free Teachers/ Tobacco-Free Society Program, focused on tobacco control policies, educational efforts, and cessation support. The control group received delayed intervention. At baseline, about one third of teachers and staff used SLT and 7% were smokers. At 30 days after the intervention, the self-reported adjusted cessation rate of SLT use was 49.6% in the intervention cohort and 15.4% in the control cohort ($P < 0.05$), whereas at 6 months, the adjusted cessation rate was 18.5% in the intervention cohort and 7.3% in the control cohort ($P = 0.06$). When the analysis was restricted to teachers who were employed at the school for the entire intervention period, the adjusted 6-month cessation rate was 20% in the intervention cohort and 6% in the control cohort ($P = 0.04$) (Sorensen et al., 2013). About 97% of the intervention schools posted "no tobacco" signboards. Also, 84.5% of the intervention schools adopted the recommended tobacco control policy; this percentage was much higher than that in the control schools (odds ratio [OR], 7.54; 95% CI, 4.92–11.60). The percentage of schools where tobacco was sold within 100 yards [~91 m] of the school decreased from 32.0% to 24.9% in the intervention schools and increased from 26.2% to 28.4% in the control schools (OR, 0.77; 95% CI, 0.54–1.11) (Mathur et al., 2016).

(c) Article 6: Price and tax measures on smokeless tobacco

Price increases and/or increased taxation on SLT products have caused a decrease in the prevalence of SLT consumption, just like for smoked tobacco products (Table 3.14).

A study conducted in the USA (Huang and Chaloupka, 2012) assessed the impact of the 2009 federal tobacco excise tax increase (effective on 1 April 2009, causing a price increase of 12%)

Table 3.14 Article 6: Effect of taxation and price increases on price elasticity for use of smokeless tobacco products with or without areca nut

Reference Location Policy	Data source (dates)	Estimated price elasticity
John (2008) India Price increase	55th round of the National Sample Survey (1999–2000)	For leaf tobacco consumption and expenditure for purchase: In rural areas: −0.871 (0.02)[a] In urban areas: −0.874 (0.03)[a]
Huang and Chaloupka (2012) USA Taxation and price increase	Monitoring the Future Surveys (2008 and 2009)	For smokeless tobacco: −1.2 to −1.8
Joseph and Chaloupka (2014) India Taxation and price increase	Global Youth Tobacco Survey, India (1999–2004)	For *gutka*: −0.58
Nargis et al. (2014) Bangladesh	International Tobacco Control-Bangladesh Wave 3 Survey (2011–2012)	For *zarda*: Lower-priced brands: −0.64 Higher-priced brands: −0.39 Cross-price elasticity with cigarettes: 0.35
Selvaraj et al. (2015) India Price increase	Consumer Expenditure Survey (2011–2012)	For leaf tobacco, by income group: Lowest income: −0.557 Middle income: −0.4537 Highest income: −0.0507

[a] Values in parentheses are bootstrapped standard errors (bidis are complements for leaf tobacco; users of one tend to also use the other).

on the use of SLT products in youth, by using two different models. The prevalence of SLT use in youth decreased from 6.06% before the tax increase to 4.22% 30 days after the tax increase – a relative decrease of 30.37% – in the first econometric model, which did not control for the other study variables. In the second model, which controlled for all the variables (such as individual, family, and school-level characteristics, state-level tobacco control measures, and state tobacco control funding), SLT use in youth decreased by 16–24%. The study also reported a price elasticity of between −1.2 and −1.8 for the prevalence of SLT use; this implies that an increase of 10% in the price of SLT products would reduce the prevalence of SLT use in youth by about 12–18% (Huang and Chaloupka, 2012).

A study on tobacco taxation and price in India (Joseph and Chaloupka, 2014), which used the GYTS data for 1999–2004 in 73 356 students aged 13–15 years, estimated the price elasticity of *gutka* as −0.58. This implies that a 10% increase in the price of a pouch of *gutka* would reduce the likelihood of someone becoming a *gutka* chewer by 5.8%.

John (2008) estimated the price elasticity for tobacco products for urban and rural households in India separately, using data from the 55th round of the National Sample Survey, conducted in 1999–2000 in 120 309 households in 10 140 villages, on tobacco consumption and expenditure incurred during the past 30 days. For both urban and rural households, the values are close to 1; this implies that a change in price (e.g. an increase due to taxation) would have a large downward effect on demand.

Another study in India (Selvaraj et al., 2015) examined the pattern of price elasticity of three major tobacco products (bidi, cigarettes, and leaf tobacco) based on household monthly per capita

consumption expenditure using data from the nationally representative Consumer Expenditure Survey of 2011–2012 in 101 662 households. The price elasticity for leaf tobacco, estimated using a simulation model, was highest in the lowest income group (−0.557), followed by the middle income group (−0.4537) and the highest income group (−0.0507). This implies that a 10% increase in tax would reduce the consumption by about 5% in the lowest income group, by about 4% in the middle income group, and by 0.5% in the highest income group (Selvaraj et al., 2015).

Nargis et al. (2014) used data from the third wave of the International Tobacco Control Survey in Bangladesh in 2011–2012 to estimate the price elasticity of the most commonly used SLT product in Bangladesh, *zarda*, and the cross-price elasticity for *zarda* with respect to cigarettes. The estimated price elasticity was −0.64 for lower-priced brands and −0.39 for higher-priced brands. This implies that a 10% increase in the price would cause a reduction in the prevalence of *zarda* use by about 6% for the lower-priced brands and by 4% for the higher-priced brands. The estimated cross-price elasticity for *zarda* with respect to the price of cigarettes was 0.35. This implies that a 10% increase in the price of cigarettes with the price of *zarda* remaining unchanged would result in an increase of about 3.5% in the consumption of *zarda*. Taken together, these estimates signify that only if the prices of both cigarettes and *zarda* were increased by 10%, a reduction of 2.5% (−6% + 3.5%) would be seen in the consumption of *zarda*.

An evaluation of the effect of the goods and services tax in India on the affordability of tobacco products revealed that all tobacco products, including SLT products, had become increasingly affordable over the previous 10 years and that the goods and services tax had accentuated the increase in the affordability of SLT products (John and Dauchy, 2021).

A meta-analysis of 17 studies on the price elasticity of demand for SLT products in 5 countries showed that a 10% price increase would reduce the demand for SLT by 2.1%. The price elasticity estimates for SLT products in high-income countries and low- and middle-income countries were similar (coefficient, −0.2) (Jawad et al., 2018). Of the 17 studies included in the meta-analysis, 2 studies (Joseph and Chaloupka, 2014; Nargis et al., 2014) are summarized above.

(d) Article 11: Packaging and labelling of smokeless tobacco products

A study in the USA (Adkison et al., 2014) evaluated the association of three elements of SLT packaging (health warning labels, descriptive characteristics, and corporate branding) with knowledge of health risks and perceptions of novelty and appeal, by using a web-based survey in 1000 individuals. Perception of health risks was higher with a graphic or pictorial health warning than with a text warning on SLT packaging for both adults and young respondents (Table 3.15).

In India, pictorial health warnings have changed substantially in content, size, and coverage during the past decade. The first pictorial health warning on SLT packages (a symbol of a scorpion), which covered < 30% of the front of the package, was released in May 2009, just before the GATS-1 (in 2009–2010) in India (MOHFW and IIPS, 2010). In a study analysing the GATS-1 India data, SLT users who thought about quitting after seeing a health warning in the past 30 days were significantly more likely to make attempts to quit compared with those who did not see a health warning (OR, 3.41; 95% CI, 3.12–3.73) (Singh et al., 2018). In 2011, the pictorial health warnings consisted of photographs of patients with oral cancer, which covered 40% of the front of all SLT packages; by 2016, these were enlarged to cover 85% of the front and the back of the package. As a result, the percentage of SLT users who noticed these health warnings increased from 62.9% in the GATS-1 to 71.6% in the GATS-2 (in 2016–2017), and the percentage

Table 3.15 Effects of text and graphic or pictorial health warning labels on smokeless tobacco packaging on perceptions of health risks

Reference Location	Study description	Perceptions of health risks (%)		
Adkison et al. (2014) USA	Cross-sectional web survey Participants (n = 1000): Youth: 14–17 yr Young adults: 18–25 yr Older adults: 26–65 yr		Text HWL	Graphic HWL
		Reduce health risks	23.2	10.8
		Consider health risks	5.4	63.6
		Most dangerous to health	4.8	28.3
		Deliver dangerous chemicals	3.9	31.8
Gravely et al. (2016) India	Tobacco Control Project India Survey from 4 states Adult SLT users (n = 4733) Policy assessed: change of HWLs from symbol to graphic images on SLT packages in 2011 Respondents who noticed HWLs (n = 2154)		Wave 1 (2010–2011) Symbolic HWL % (95% CI)	Wave 2 (2012–2013) Graphic HWL % (95% CI)
		Among all respondents (n = 4733):		
		Aware that SLT packages contain HWLs	72.7 (67.1–77.7)	73.0 (67.3–78.1)
		Noticed HWLs at least once in a while	34.3 (28.5–40.6)	28.1 (21.8–35.4)
		Among respondents who noticed HWLs (n = 2154):		
		Read HWLs at least once in a while	49.4 (42.0–56.9)	50.1 (40.4–59.9)
		HWLs made you think about risks of SLT at least a little	15.0 (11.9–18.8)	17.5 (12.1–24.6)
		HWLs made you think about quitting SLT at least a little	16.8 (13.0–21.4)	19.3 (13.6–26.6)
		Avoided looking at HWLs	8.1 (5.5–11.8)	11.6 (7.8–17.0)
		Gave up SLT use at least once because of HWLs	31.3 (24.3–39.3)	36.7 (27.2–47.5)
		Have any intentions to quit SLT use	19.8 (14.6–26.4)	20.5 (15.2–27.0)
MOHFW and IIPS (2010); TISS and MOHFW (2017) India	Cross-sectional national survey: Global Adult Tobacco Survey		GATS-1 (2009–2010) Photograph warning covering 40% of front of package	GATS-2 (2016–2017) Photograph warning covering 85% of front and back of package
		Noticed HWLs	62.9	71.6
		Thought of quitting because of the HWLs	33.8	46.2

CI, confidence interval; GATS, Global Adult Tobacco Survey; HWL, health warning label; SLT, smokeless tobacco; yr, year or years.

of SLT users who thought of quitting also increased, from 33.8% in the GATS-1 to 46.2% in the GATS-2 (TISS and MOHFW, 2017).

Gravely et al. (2016) evaluated the impact of the change in the health warning labels on SLT packaging from a single symbol (a scorpion) in 2009 to four new graphic images in 2011, using data from the Tobacco Control Project India Survey (wave 1 in 2010–2011 and wave 2 in 2012–2013) from 4 states (Bihar, West Bengal, Madhya Pradesh, and Maharashtra) in 4733 individuals aged ≥ 15 years. The change from a symbol to graphic images did not significantly increase any of the health warning label indicators or intentions to quit SLT use. However, people who quit using SLT were significantly more aware of health warning labels compared with people who continued to use SLT.

A study in 99 tobacco users (smokers and SLT users) in Chennai, India, assessed the impact of the pictorial health warnings (photographs of throat cancer on cigarette packages and of oral cancer on SLT packages, covering 85% of the front and back of the package) on the motivation of tobacco users to quit. Most (84.8%) of the tobacco users noticed the health warning labels (including the text warning); 21.2% of SLT users were able to identify the picture correctly, and 55.5% of tobacco users could relate the pictures to health problems. Including pictorial health warnings made 52.5% of users think about quitting, and 72.7% said that these warnings would motivate them to quit tobacco use. Because the text warning was only in English, not everyone could read it, but those who could not read the text understood the pictorial warning (Bincy et al., 2018).

(e) Article 12: Education, communication, training, and public awareness on smokeless tobacco

In a study analysing the GATS-1 India data, SLT users who noticed anti-SLT messages were significantly more likely to make attempts to quit compared with those who did not notice these messages (OR, 1.42; 95% CI, 1.30–1.56) (Singh et al., 2018).

In 2009, a national mass media communication campaign on the dangers of SLT use, called the Surgeon campaign, aired on television and radio in India for 6 weeks (Murukutla et al., 2012) in three languages (Hindi, English, and Sindhi) (Vital Strategies, 2010). A nationally representative survey was subsequently conducted to evaluate the impact of the campaign in SLT users aged 16–50 years who had access to television or radio during the previous 2 months. The survey was administered to 2108 users of SLT only and 790 SLT users who also smoked (dual users). Of these, 1323 users of SLT only (62.8%) and 565 dual users (71.5%), or a total of 1888 users (65.1%), were aware of the campaign. Of the respondents who were aware of the campaign, 62% recalled the campaign on television only, 21% on both television and radio, and 16% on radio only. Of the campaign-aware respondents, 72% said that the campaign made them stop and think. Almost 75% of the users of SLT only and 77% of the dual users said that the campaign made them feel concerned about the effects of using SLT on their health. In a logistic regression analysis, users of SLT only who were aware of the campaign were 2.4 times as likely to say that SLT causes mouth cancer ($P < 0.001$) compared with those who were not aware of the campaign, and they were more likely to agree that quitting SLT use would improve their health. Dual users who were aware of the campaign were 2.3 times as likely to say that SLT causes throat cancer ($P < 0.001$). When respondents were asked about non-campaign-relevant statements (e.g. "SLT use by pregnant women causes low-birth-weight babies"), there was little or no difference in the responses between those who were aware of the campaign and those who were not. Users of SLT only who were aware of the campaign were more likely to have seriously considered quitting SLT use in the previous 2 months (OR, 1.6; $P < 0.001$)

and were more likely to have attempted to quit in the previous 2 months (OR, 1.9; $P < 0.001$) compared with those who were not aware of the campaign.

After the Surgeon campaign, a new campaign was developed based on the story of Mukesh, a young patient (age 24 years) who died of oral cancer. The campaign consisted of a 30-second video message of Mukesh speaking to the public from his hospital bed, after an introduction by the surgeon. Subtitles were used in different languages. The video was aired for 4 weeks in 2011 by the Government of India. Apart from public awareness, the Mukesh campaign also provided a face and a story for advocacy and policy efforts about the harms of SLT use (including the request for a ban on *gutka*, as part of the Voice of Tobacco Victims campaign spearheaded by surgeons from Tata Memorial Hospital in Mumbai, India). The Mukesh campaign was evaluated using street intercept interviews of tobacco users in 5 states representing 5 zones of India. The findings showed that 71% of SLT users recalled the campaign, 80% rated it as believable, 79% found it personally relevant, and 77% said it made them feel concerned about the health effects of their own SLT use (Vital Strategies, 2011; Gupta et al., 2016a).

In 2016, a mass communication campaign, called the People Behind the Packs campaign, was started in Bangladesh, in Bengali and English, to support the introduction of pack-based graphic warning labels and persuade tobacco users (including SLT users) to heed the warnings in order to avoid the depicted tobacco-related diseases. Two of the messages from the communication campaign aired on 13 national television stations, and all 4 messages were portrayed on billboards and community health centre posters. A cross-sectional face-to-face survey was conducted within 14 days of the television campaign in 1796 adult tobacco users (including SLT users) aged 16–55 years. The results showed that 66.5% of users were aware of at least one People Behind the Packs campaign message, 83.6% had seen the new graphic warning labels on tobacco packaging, and 38.1% had made an attempt to quit. Attempts to quit were significantly associated with having seen the new graphic warning labels on tobacco packaging ($P < 0.001$), recalling at least one People Behind the Packs campaign message ($P < 0.001$), and recalling a greater number of adverse effects of using tobacco products ($P < 0.001$). However, attempts to quit were less likely in users of SLT only ($P < 0.001$) and in dual users ($P < 0.01$) than in smokers (Turk et al., 2018).

(f) Article 13: Ban on smokeless tobacco advertising, promotion, and sponsorship (TAPS)

There is a dearth of studies on the impact of policies to prohibit advertising and sponsorship of SLT on quitting or attempts to quit SLT use.

A cross-sectional study in Mumbai, India, in 1373 high school students and 436 tobacco vendors close to their schools reported a lower risk of current SLT use in students at schools in areas with higher compliance by vendors with tobacco point-of-sale policies (OR, 0.40; 95% CI, 0.21–0.77) compared with students at schools in areas with lower compliance, when controlling for student-level and community-level tobacco use risk factors (Mistry et al., 2019).

A cross-sectional study in 1670 students aged 13–15 years was conducted in 28 randomly selected schools in 7 areas of Khartoum in the Sudan. The students completed a questionnaire about their exposure to *toombak* advertisements at point of sale, the social acceptability of *toombak* use, the perceived accessibility of *toombak*, susceptibility to *toombak*, and *toombak* use. Despite a legal ban on advertisement at point of sale, 41.8% of students reported exposure to *toombak* advertisements at point of sale. Exposure to such advertisements was associated with male sex, older age, ever use, more social

acceptability, and direct accessibility of *toombak* (Almahdi et al., 2020).

(g) Article 14: Demand reduction measures concerning smokeless tobacco dependence and cessation

In Oklahoma (USA), a state with a high prevalence of SLT use, a sample of 959 male users of SLT only who had registered with the Oklahoma Tobacco Helpline in 2004–2012 were assessed for factors related to SLT abstinence (Mushtaq et al., 2015). Of the 374 SLT users who completed the 7-month follow-up, 162 (43%) reported 30-day abstinence, representing a 15% cessation rate. SLT users with higher levels of motivation to quit at baseline were twice as likely to be abstinent than those with low or moderate levels of motivation to quit (OR, 2.05; 95% CI, 1.25–3.35), and each additional completed helpline call increased the likelihood of tobacco cessation by 20%.

In Rajasthan, India, a quitline service was initiated in January 2013 as a voluntary activity (Gupta et al., 2016b) and later became a part of the 104 Information Helpline of the Medical and Health Department of the Government of Rajasthan. Of the 1525 callers in 2013, 1105 (72.5%) were SLT users. A self-reported cessation rate of about 20% was observed in the SLT users at the 18-month follow-up. This is > 11 times the cessation rate of 1.6% for former daily users of SLT (and former daily smokers) in Rajasthan reported in the GATS-1.

A national tobacco quitline was started in May 2016 in India. Of the 5179 callers who registered during the first year (Kumar et al., 2018), 3169 (61.2%) were SLT users and 644 (12.4%) were dual users. When the dual users were excluded, 41% of SLT users successfully quit (complete abstinence for ≥ 3–4 weeks). After the national quitline number was included on tobacco packages, from September 2018, the percentage of callers who were SLT users increased from 51.1% to 70.7%, the number of tobacco users registering with the quitline increased 3.3-fold, and the number of quitters increased 3.6-fold at 6 months (Kumar et al., 2021).

(h) Article 16: Access to and availability of smokeless tobacco to minors

Although 174 countries have restrictions in place to prevent minors from purchasing tobacco (including SLT products) (WHO, 2021b), no evidence is available about adequate enforcement of this policy or its efficacy (Choi et al., 2014; Khan, 2016; Huque et al., 2017; Nyi Latt et al., 2018; Cho et al., 2020).

In July 1992, the United States Congress enacted the Alcohol, Drug Abuse, and Mental Health Administration Reorganization Act (Public Law 102-321). Through the Synar Amendment to this law, the sale or distribution of any form of tobacco to minors (aged < 18 years) was prohibited. The 2014 Annual Synar Report in 50 states and 8 jurisdictions reported a decrease in the sales of all tobacco to minors (aged < 18 years), from 40.1% in 1997 to 9.6% in 2013 (national weighted averages). Also, the states that fined retailers for selling tobacco to minors had fewer violations of the Synar Amendment (SAMHSA, 2014).

(i) Bans on smokeless tobacco products

This section discusses studies that reported the impact of the prohibition of sale, manufacture, and importation of SLT on its consumption and the quit intentions of users, in some high-burden countries (i.e. those with > 1 million users or a prevalence of ≥ 10% in males or females) (Mehrotra et al., 2017).

Among the high-burden countries, Thailand was the first to impose a ban on the importation of SLT, in 1992, and the country undertook stringent measures for compliance with the ban. The tobacco control programme in Thailand contributed to a decrease in the prevalence of SLT use in adults from 3.9% (1.3% in men and 6.3% in women) in 2009 (WHO Regional Office for South-East Asia, 2009b) to 3.2% (1.1% in men

Table 3.16 Impact of the *gutka* ban on the prevalence of *gutka* use in India[a]

Reference Location	Prevalence of *gutka* use (%)						Relative change in prevalence of use (%)		
	Before the ban: GATS-1[b] (2009–2010)			After the ban: GATS-2[b] (2016–2017)					
	Overall	Men	Women	Overall	Men	Women	Overall	Men	Women
MOHFW and IIPS (2010); TISS and MOHFW (2017) India	8.2	13.1	2.9	6.8	10.8	2.7	–17.1	–17.6	–6.9

GATS, Global Adult Tobacco Survey.
[a] The *gutka* ban was implemented in 2012.
[b] Repeated cross-sectional household survey of individuals aged ≥ 15 years, with a multistage, geographically clustered sample design.

and 5.2% in women) in 2011 (WHO Regional Office for South-East Asia, 2011) and 2.1% in 2017 (National Statistical Office of Thailand, 2017).

In India, a central law in 2011 prohibited tobacco or nicotine from being used in any food products (MOHFW, 2011c), which led to a subsequent statewise ban on the manufacture, storage, and sale of *gutka*. A resultant decrease was observed in the prevalence of *gutka* use, from 8.2% in the GATS-1 to 6.8% in the GATS-2 (Table 3.16). However, *gutka* continued to be available illegally, including near educational institutions (Pimple et al., 2014).

A study conducted in 2014 to assess the impact of the *gutka* ban in the Indian states of Assam, Bihar, Gujarat, Karnataka, Madhya Pradesh, Maharashtra, Odisha, and Delhi (National Capital Region) revealed that 92% of the population supported the ban and 99% agreed that it was good for the youth of the country (WHO Regional Office for South-East Asia, 2014). Interviews with 1001 current and former users of *gutka* revealed that 49% of current users had reduced their consumption and the remaining 51% had attempted to stop using *gutka* in the previous year. About 41–88% of respondents across the different states reported quitting *gutka* use as a result of the ban.

A study in Maharashtra, India, in 68 *gutka* users (Mishra et al., 2014) found that since the ban, 24% had quit *gutka* use, 56% had reduced their consumption, and 21% had not changed their consumption; none of the participants reported an increase in their use of *gutka*. Some respondents had turned to products that are custom-made by vendors and contain similar ingredients (e.g. *mawa*, betel quid) or to another commercially available SLT product (*khaini*).

A study conducted in Andhra Pradesh, India, in 368 *gutka* users (Reddy et al., 2016) reported that most of the users (81.5%) had tried to quit *gutka* use and 29.9% of the users had turned to other forms of SLT products, most commonly *mawa* (51.8%). Also, 62.2% of the users reported that *gutka* was still available commercially in the form of two separate sachets, one of *paan masala* and the other of tobacco.

In Bhutan, despite a comprehensive ban on the cultivation, manufacture, distribution, and sale of tobacco since 2004, the prevalence of use of tobacco, especially SLT, is high. A cross-sectional analysis of the nationally representative Noncommunicable Disease Risk Factors Surveillance STEPS Survey 2014 in 2820 adults in Bhutan showed a high prevalence of SLT use (19.7%; 95% CI, 16.5–22.9%), especially in males, younger individuals, and people who consumed

alcohol (Gurung et al., 2016). An increase in SLT use in adolescents was also noted in the GYTS in Bhutan, from 18.8% in 2006 to 30.3% in 2013 (WHO Regional Office for South-East Asia, 2015).

Since 1992, there has been a ban on the sale of tobacco for oral use (i.e. *snus*) in the EU except in Sweden (Delhomme, 2019). From 2001, the European Commission reaffirmed that the EU Member States were prohibited from placing tobacco for oral use on the market (Article 8 of Directive 2001/37/EC) (European Parliament, 2001). However, this ban has been evaded through online sale and promotion of *snus* in the EU (Peeters and Gilmore, 2013).

(j) Overall tobacco control policy and Article 20: Research, surveillance, and exchange of information on smokeless tobacco

Standard, nationally representative surveys designed to measure tobacco use and the impact of tobacco control policies in countries in an internationally comparable way were developed jointly by the United States Centers for Disease Control and Prevention and WHO. These surveys include the GYTS, the GSPS, the Global Health Professions Student Survey, and the GATS, which together make up the Global Tobacco Surveillance System.

The GATS is a household survey that is administered in male and female individuals aged ≥ 15 years. A few of the countries with a high SLT burden in the WHO South-East Asia Region, such as Bangladesh, India, and Thailand, have completed two rounds of the GATS since 2009 (WHO Regional Office for South-East Asia, 2009a, b, 2011; MOHFW and IIPS, 2010; TISS and MOHFW, 2017; Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019) (Table 3.17). In all three countries, the prevalence of SLT use decreased significantly between the GATS-1 and the GATS-2: in Bangladesh, from 27.2% in 2009 to 20.6% in 2017; in India, from 25.9% in 2009–2010 to 21.4% in 2016–2017; and in Thailand, from 3.9% in 2009 to 3.2% in 2011 (Suliankatchi Abdulkader et al., 2019) (Table 3.17). After the GATS-1 in Bangladesh, pictorial health warnings were introduced that covered 50% of SLT packages, anti-SLT media campaigns were conducted, direct marketing of SLT was prohibited, and taxation of SLT products increased (Bangladesh Bureau of Statistics and National Tobacco Control Cell, 2019). In India, the ban on the manufacture and sale of *gutka* was implemented in 2012. In Thailand, since 2009 pictorial health warning labels are also required on packaging of shredded tobacco products (used as SLT) (WHO Regional Office for South-East Asia, 2011).

The GYTS is a school-based survey of students aged 13–15 years. Between 2007 and 2013, the prevalence of current SLT use did not change significantly in Bangladesh, India, or Myanmar, but the prevalence increased significantly in Bhutan and Nepal. During this period, there was either an absence of effective policies focusing on SLT control or a lack of enforcement of policies in these countries. For instance, in India, where the Cigarettes and Other Tobacco Products Act was enacted in 2004, a few court cases by the tobacco industry prevented adequate implementation of the legislation for several years. In Nepal, a tobacco control policy was enacted in 2010, but litigation by the tobacco industry continued until 2014 (Sinha et al., 2014).

From 2010, the Tobacco Control Act of Bhutan (Parliament of Bhutan, 2010) prohibited the cultivation, manufacture, sale, and supply of tobacco products; it remained in effect until 2020 (Wangdi and Gyeltshen, 2020). Awareness programmes on the dangers of tobacco were also undertaken in Bhutan (Tshering et al., 2021). In Sri Lanka, from 2006, the tobacco control law prohibited the sale of tobacco to minors (aged < 21 years) (Sinha et al., 2014). In Nepal, tobacco control laws in 2011 required graphic health warnings covering 75% of both the front and the back of the package for all tobacco products;

Table 3.17 Reduction in prevalence of smokeless tobacco use in adults after policy interventions in selected countries

Reference Location	GATS-1[a]		GATS-2[a]		Reduction in prevalence of SLT use[b] (relative change) (%) Overall (men; women)	Policies and population-level interventions
	Year No. of households surveyed	Prevalence of SLT use[b] (%) Overall (men; women)	Year No. of households surveyed	Prevalence of SLT use[b] (%) Overall (men; women)		
WHO Regional Office for South-East Asia (2009a); Bangladesh Bureau of Statistics and National Tobacco Control Cell (2019) Bangladesh	2009 10 751	27.2 (26.4; 27.9)	2017 14 880	20.6 (16.2; 24.8)	–24.1* (–38.6*; –11.3) * $P < 0.05$	Pictorial health warnings to cover 50% of SLT packages, anti-SLT media campaigns; marketing of SLT prohibited, and increased taxation of SLT products, verified by tax stamp
MOHFW and IIPS (2010); TISS and MOHFW (2017) India	2009–2010 69 296	25.9 (32.9; 18.4)	2016–2017 77 170	21.4 (29.6; 12.8)	–17.4 (–10.0; –30.4) $P < 0.01$	Manufacture and sale of *gutka* and *paan masala* containing tobacco or nicotine banned by nearly all states by 2012 under national law; taxes on SLT increased marginally; public awareness campaigns on SLT in different media; in 2012, tobacco use in films was regulated; in 2016, pictorial health warnings were enlarged to 85% of both principal display areas on packages
WHO Regional Office for South-East Asia (2009b, 2011) Thailand	2009 22 768	3.9 (1.3; 6.3)	2011 20 922	3.2 (1.1; 5.2)	–17.2 (–18.0; –17.0) $P < 0.05$	Pictorial health warnings and text warnings on tobacco packages; taxation

GATS, Global Adult Tobacco Survey; SLT, smokeless tobacco.

[a] Repeated cross-sectional household survey of individuals aged ≥ 15 years, with a multistage, geographically clustered sample design.

[b] SLT use includes use of SLT only and SLT use plus smoking; prevalence of current use includes daily and occasional use.

this was implemented in 2014 (Sinha et al., 2014). In Myanmar, tax rates for tobacco products, including SLT, increased in 2012 and again in 2015 (World Bank Group, 2020), and from 2016 the size of health warnings on SLT and smoked tobacco products was increased to 75% of both the front and the back of the package (Tun et al., 2017; Campaign for Tobacco-Free Kids, 2021),

After 2014, the prevalence of SLT use in youth decreased in four countries with a high SLT burden: in Bhutan, from 21.6% in 2013 (Sinha et al., 2014; WHO Regional Office for South-East Asia, 2015) to 12.5% in 2019 (WHO Regional Office for South-East Asia, 2020); in India, from 14.0% in 2003 to 4.1% in 2019 (MOHFW and IIPS, 2019); in Myanmar, from 9.8% in 2011 (Sinha et al., 2014) to 5.7% in 2016 (Tun et al., 2017); and in Sri Lanka, from 8.5% in 2011 to 2.4% in 2015 (WHO Regional Office for South-East Asia, 2016) (Table 3.18). In Bhutan in the GYTS 2019, 87.1% of current SLT users wanted to stop using it right away. In Bhutan, according to law, tobacco cannot be cultivated and tobacco products cannot be produced. Although tobacco products can be imported for personal consumption, there are limits on the amounts, and importation is prohibited for minors (aged < 18 years). The advertisement, promotion, and sponsorship of tobacco are banned, except for brand stretching (WHO Regional Office for South-East Asia, 2020).

A survey was conducted in two waves, in 2009 and 2010, in 755 school personnel in 72 state government schools in Bihar, India (Gupta et al., 2014a). The reported prevalence of current use of tobacco (mainly SLT) was 35.5% (48.0% in men and 11.3% in women), which was much lower than the prevalence of 77.4% previously reported in the GSPS 2000. Use of *lal dant manjan* (red tooth powder) was considered as use of a tobacco product in the GSPS 2000 but not in this school study, because the inclusion of tobacco in any oral hygiene products was prohibited by a government order. If use of *lal dant manjan* was included as tobacco use in the school survey, the prevalence of tobacco use would increase to 53.9%, which is still substantially lower than the prevalence in the GSPS 2000 (Gupta et al., 2014a).

(k) Modelling the impact of a set of policies using available data

In a study conducted in Minnesota (USA), Levy et al. (2019) estimated the effect of tobacco control policies implemented in 1993–2018 on SLT use using a previous SimSmoke model, updated and extended to incorporate SLT use (both use of SLT only and dual use) (Table 3.19). The SimSmoke model projected that the prevalence of SLT use in men would decrease from 3.9% in 1993 to 2.6% in 2015 and to 2.5% in 2018. In addition, compared with no new policies implemented after 1993, the model projected that the prevalence of SLT use in men would decrease to 2.9% in 2040 (Levy et al., 2019). The Minnesota Adult Tobacco Survey conducted in 2014 reported only a slight decrease in the prevalence of SLT use, to 3.6% (Boyle et al., 2015); this was contradictory to the decrease predicted by the model.

The SimSmoke model was also used to assess the effect of past tobacco control policies and to project the effect of future policies on the prevalence of *snus* use (and smoking) in Sweden (Near et al., 2014; Table 3.20). The model predicted that if all of the policies were implemented, the prevalence of use of *snus* only would decrease from 14.6% in 2010 to 10.4% in 2040 in men and from 3.3% in 2010 to 2.8% in 2040 in women. Overall, the study showed that a combination of the policies would have a greater impact on the prevalence of SLT use than a single policy. According to a survey in 2010, the overall prevalence of SLT use [SLT product not specified] in Sweden was 12.3% (20.7% in men and 3.5% in women) (Leon et al., 2016).

Table 3.18 Reduction in prevalence of smokeless tobacco use in students aged 13–15 years after policy interventions in selected countries

Reference Location	Earlier GYTS[a]		Later GYTS[a]		Reduction in prevalence of SLT use[b] (relative change (%) Overall (boys; girls)	Policies and population-level interventions
	Year	Prevalence of SLT use[b] (%) Overall (boys; girls)	Year	Prevalence of SLT use[b] (%) Overall (boys; girls)		
MOHFW and IIPS (2019) India	2003	14.0 (18.0; 7.9)	2019	4.1	–70.7	Cigarettes and Other Tobacco Products Act (COTPA) in 2004; ban on the manufacture and sale of *gutka* in 2012
Sinha et al. (2014); WHO Regional Office for South-East Asia (2020) Bhutan	2013	21.6 (25.0; 18.9)	2019	12.5 (17.0; 8.1)	–42.1 (–32.0; –57.1)	Tobacco Control Amendment Act of 2012 to the Tobacco Control Act of Bhutan of 2010; Tobacco Control Rules and Regulations 2013. The rules prohibit minors (aged < 18 years) from importing tobacco or tobacco products, even for personal consumption. However, SLT is available and accessible to youth
Sinha et al. (2014); Tun et al. (2017); Campaign for Tobacco-Free Kids (2021) Myanmar	2011	9.8 (15.2; 4.0)	2016	5.7 (11.0; 1.5)	–41.8 (–27.6; –62.5)	From 2016, the size of health warnings on SLT and smoked tobacco products was increased to 75% of the front and back of the package
Sinha et al. (2014); WHO Regional Office for South-East Asia (2016) Sri Lanka	2011	8.5 (13.0; 4.1)	2015	2.4 (4.2; 0.5)	–71.8 (–67.7; –87.8)	The school curriculum has contained lessons on the harmfulness of tobacco use (mainly smoking) for several years, before these surveys

GYTS, Global Youth Tobacco Survey; SLT, smokeless tobacco.

[a] Repeated cross-sectional national school-based, self-administered survey of students aged 13–15 years, with a two-stage sample design.

[b] SLT use includes use of SLT only and SLT use plus smoking; prevalence of current use includes daily and occasional use.

Table 3.19 Modelling projections of the impact of tobacco control policies on prevalence of smokeless tobacco use in men in Minnesota (USA) for 1993–2040

Reference Location	Study design	Tobacco control policies	Prevalence of SLT use in men[a] (%)		
			Actual	Projection Best (lower, upper)[b]	
			1993	2018	2040
Levy et al. (2019) Minnesota (USA)	SimSmoke modelling to estimate the impact of policies on SLT use Period of policies included in model: 1993–2018 Used data from the 1993 Tobacco Use Supplement and information on state policies	Policies remaining at 1993 levels	3.9	3.2 (3.2, 3.2)	2.9 (2.9, 2.9)
		All policies (cumulative)	3.9	2.5 (2.8, 2.2)	2.1 (2.4, 1.8)
		Price policies	3.9	2.8 (2.9, 2.6)	2.5 (2.6, 2.3)
		Smoke-free air policies	3.9	3.2 (3.2, 3.1)	2.8 (2.9, 2.8)
		Tobacco control expenditure by state	3.9	3.1 (3.2, 3.1)	2.8 (2.8, 2.8)
		Cessation treatment	3.9	3.1 (3.1, 3.0)	2.8 (2.8, 2.7)
		Health warnings policies	3.9	3.2 (3.2, 3.1)	2.8 (2.9, 2.8)
		Youth access policies	3.9	3.1 (3.2, 3.1)	2.7 (2.8, 2.6)

SLT, smokeless tobacco.

[a] According to the model, projected prevalence rates for SLT use in women were not affected by the policies.

[b] Estimates are given in terms of the best estimate and the lower and upper bounds based on the policy evaluation literature.

Table 3.20 Modelling projections of the impact of tobacco control policies on prevalence of *snus* use in Sweden

Reference Location	Study design	Tobacco control policies	Prevalence of use of *snus* only (%) Projections for 2010–2040							
			Men				Women			
			2010	2011	2020	2040	2010	2011	2020	2040
Near et al. (2014) Sweden	SimSmoke modelling to estimate the impact of policies on prevalence of use of *snus* only Used data from the Health on Equal Terms of the National Public Health Survey for 2004–2010	Status quo	14.6	14.5	14.4	13.5	3.3	3.3	3.5	3.6
		Newly implemented policies[a]								
		Raise excise taxes to 70% of retail price	14.6	13.4	13.1	11.9	3.3	3.0	3.1	3.1
		Complete smoke-free	14.6	14.5	14.4	13.5	3.3	3.3	3.5	3.6
		Comprehensive marketing ban	14.6	14.4	14.2	13.3	3.3	3.3	3.4	3.5
		High-intensity tobacco control campaign	14.6	14.1	13.8	12.9	3.3	3.2	3.3	3.4
		Strong health warnings	14.6	14.5	14.3	13.4	3.3	3.3	3.4	3.5
		Strong youth access enforcement	14.6	14.5	14.1	12.8	3.3	3.3	3.4	3.4
		Cessation treatment policies	14.6	14.5	14.2	13.3	3.3	3.3	3.4	3.5
		All of the above policies implemented	14.6	12.7	12.0	10.4	3.3	2.9	2.9	2.8

[a] New policies implemented at levels consistent with the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) in 2010 and maintained at the same level until 2040.

3.4.2 Control policies for areca nut products (including betel quid)

Areca nut is cultivated and consumed mainly in South and South-East Asia. In the past few decades (1994–2019), there have been increases in the global production, which is highest in India, followed by Bangladesh, Indonesia, Myanmar, and Taiwan (China), and in areca nut consumption and trade (FAO, 2021). The increase in consumption of areca nut in different forms has led to high incidence rates of oral cancers and oral potentially malignant disorders, especially in India (Gupta et al., 2014b), Hunan (China) (Zhou et al., 2019), Taiwan (China) (Su et al., 2020), Bhutan, Myanmar, Nepal, Papua New Guinea, Pakistan, Sri Lanka, and various South Pacific islands such as Guam (USA) and the Solomon Islands (Gunjal et al., 2020). This, in turn, has led to the adoption in several countries over the past several decades of policies designed to control use of areca nut (Table 3.21).

Areca nut control policies began in Thailand in 1940 with a campaign promoted by the prime minister to discourage betel quid chewing, showing that streets stained with red juice from spitting were dirty and unhygienic, and prohibiting betel quid chewing on government premises (Thai Cultural Encyclopedia Foundation, 1999). Currently, the most common policy to curb areca nut consumption as well as SLT use is a ban on spitting in public places; this has been adopted by several countries, most recently in India during the COVID-19 pandemic (Gunjal et al., 2020; The Economic Times, 2020; Yang et al., 2020). The next most common policy is a ban on betel quid chewing in certain places, such as government offices, schools, and hospitals,

Table 3.21 Major areca nut control policies and where they have been adopted

Policy[a]	Locations
Ban on spitting in public places	Bhutan, Myanmar, Papua New Guinea, India (by the railways only), Taiwan (China), Hangzhou City (China)
Ban on chewing betel quid in certain places	Myanmar (in or near government offices, schools, and hospitals), Sri Lanka, Taiwan (China) (in the military and in some workplaces)
Ban on advertising of areca nut products	Hunan Province (China)
Ban on manufacture and/or sale of certain areca nut products	India, Sindh Province (Pakistan), Xiamen in Fujian Province (China), Myanmar
Text warnings on packages of areca nut products	India
Betel quid cessation programmes	Taiwan (China)
Mass media awareness programmes	Myanmar, Taiwan (China)
Plantation programme	Taiwan (China)
Oral mucosal screening programme	Taiwan (China)

[a] In most countries, betel quid usually also contains tobacco.
Compiled by the Working Group, with data from Vital Strategies (2017); Zhou et al. (2019); Gunjal et al. (2020); The Economic Times (2020); Yang et al. (2020); Zhao and Davey (2020).

in the military, or in certain other workplaces (Gunjal et al., 2020). There have also been mass media awareness programmes about the dangers of betel quid chewing in Taiwan (China) (Yang et al., 2020) and in Myanmar (Vital Strategies, 2017). Currently, Taiwan (China) has the highest number of areca nut control policies, followed by Myanmar and India.

In Taiwan (China), a national areca nut and betel quid cessation programme has been implemented since the late 1990s (Yang et al., 2020). From 1997, 3 December was declared Areca Prevention Day, to raise awareness of the carcinogenicity of areca nut through mass media communication, school programmes, and health-care providers. The government and nongovernmental organizations have created areca nut-free environments to promote healthy behaviour and support a reduction in use of betel quid and areca nut in the community. Beginning in 2014 in Taipei (Hsu, 2014), spitting of betel quid juice in public places has been prohibited under the Waste Disposal Act and enforced by the Environmental Protection Administration (Yang et al., 2020). Support for areca nut cessation has been implemented with culturally sensitive educational materials, especially in high-risk communities and workplaces. An oral mucosal screening programme is available for chewers, former chewers, and smokers (Yang et al., 2020). Also, clothing restrictions have been introduced for the previously scantily clad young women (called "betel quid beauties") who sell areca nut at neon-lit stalls that are frequented by taxi drivers, truck drivers, and other workers (Nylander, 2016). In 2014, the Council of Agriculture introduced a plantation programme that helped areca nut growers change to other cash crops; this led to a reduction of 5% in the area cultivated and of 18% in production. Since the start of such areca nut prevention efforts, the prevalence of betel quid chewing in adults (aged ≥ 18 years) has decreased steadily in all age groups, from about 45% in 2007 to about 5% in 2018. Also, the annual incidence rate of oral cancer has plateaued since 2009 at just more than 42 per 100 000 people,

after increasing for several decades (Yang et al., 2020).

In India, there is a provision under the Food Safety and Standards Act, 2006 (Ministry of Law and Justice, 2006) for the prohibition of the manufacture, storage, distribution, or sale of any article of food product for up to 1 year. This has been used in some states to prohibit *paan masala* (primarily see table containing areca nut). There is also a restriction on the use of anticaking agents, such as magnesium carbonate, in food products (MOHFW, 2011a). This restriction has been used in some states to ban *paan masala*, which invariably contains magnesium carbonate. Also, since 1990, packages of *paan masala* and *supari* have text health warnings (MOHFW, 2011b; NIHFW, 2014). *Gutka*, which consists of areca nut with tobacco, has been banned statewise in India since 2012 (Gunjal et al., 2020).

In China, the first step towards regulating areca nut was a 2019 ban on advertising of areca nut products by companies based in Hunan (Zhou et al., 2019). Also, another city in China (Xiamen, in Fujian Province) adopted a specific anti-areca nut policy that banned the production, sale, and use of areca nut (Zhao and Davey, 2020).

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4. SCREENING AND EARLY DIAGNOSIS OF ORAL CANCER

4.1 Screening methods and technologies

4.1.1 Clinical oral examination

The first-line approach to the identification of oral cancer and oral potentially malignant disorders (OPMDs) remains the standard clinical oral examination (COE). Traditionally, COE consists of a white-light visual examination and palpation of the oral cavity structures and the external facial and neck regions.

A routine can be established to examine each oral anatomical subsite in a consistent way. For example, one would first examine the lips/labial mucosae, the buccal mucosae, and the buccal aspects of the mandibular and maxillary gingivae, and then the lingual aspects of the mandibular gingivae, followed by examination of the palate (hard and soft), the floor of the mouth, the tongue, and the tonsils. A detailed description of how to examine the oral cavity for cancer is available in Ramadas et al. (2008b).

COE involves both a visual examination and a tactile examination (i.e. digital palpation). The neck is examined to identify enlarged lymph nodes or masses. There is no universally recognized, evidence-based determination of what constitutes an appropriate oral cancer screening examination. Li et al. (2013) described an expert consensus on what should be included in the cancer screening process for the general population in the USA. Abnormal oral mucosal findings indicative of oral cancer or OPMDs will lead to referral for further evaluation (Warnakulasuriya, 2020).

(a) Necessary training

Expertise in the screening and diagnosis of oral mucosal diseases varies substantially across different clinicians and community workers engaged in either organized or opportunistic screening activities, and these differences are linked to their different training backgrounds. A meta-analysis of eight studies comparing the knowledge, attitudes, and practices of dentists and physicians related to oral cancer and OPMDs concluded that dentists were better trained than physicians to perform COE and to recognize white or red lesions (Coppola et al., 2021). Educational requirements for competence in performing oral cancer screening are not universal, but they have been formalized in some countries, including the USA, where the Commission on Dental Accreditation has mandated that all graduating dentists be competent in performing screening for oral cancer. Such competencies are not mandated for medical school graduates, and the results from a survey showed variable training across medical schools in the United Kingdom (Carter et al., 2011).

The need to improve training for medical providers to perform COE was suggested long ago (Carter and Ogden, 2007; Shanks et al., 2011), and in one study most of the survey respondents indicated a desire for further education on the identification of oral cancer (Ni Riordain and McCreary, 2009). Interventions to train medical practitioners have been associated with improvements in knowledge, attitudes, and practices over the short term (Papadiochou et al., 2020). Web-based educational approaches seem feasible to facilitate teaching primary health-care workers to perform COE (Wee et al., 2016).

In terms of allied clinicians, dental hygienists may play a primary role in performing opportunistic COE at recall visits in dental offices (Clarke et al., 2018). Similar to the situation for medical education, nurses and nurse practitioners receive variable education on oral cancer screening (Carter et al., 2009). The perceived benefit of such education has been recognized (Patton et al., 2006; Li et al., 2020). In low-resource countries, there is evidence that community health-care workers can be successfully trained to perform oral cancer screening (Warnakulasuriya and Kerr, 2021).

Even though dentists receive training on performing COE and recognizing abnormalities, there is evidence to suggest that they often lack the skills to identify early lesions (Maybury et al., 2012) and that they may lack the decision-making skills to differentiate oral cancers and OPMDs from benign lesions (Kerr et al., 2020).

(b) Performance of COE

A recent analysis of nine studies (10 data sets) assessed the accuracy of COE to detect oral cancer and OPMDs (Walsh et al., 2021b). These studies varied widely in terms of the types of primary screeners performing COE (non-expert community health-care workers, dentists, physicians, or nurses), the settings in which the studies were performed, the definition of what constitutes a positive or negative finding, and the reference standard against which the results of COE performed by the primary screener were compared (clinical diagnosis by an expert and/or histological end-points). In all the studies, screeners were trained to perform COE. A negative COE finding was designated when the patients either had no discernible abnormality or had an abnormality that was deemed to be benign. Compared with the reference standard, non-expert screeners who designated the COE findings as negative performed very well (pooled specificity, 98%; 95% confidence interval [CI], 97–100%) (Table 4.1). The small overall false-positive rate (1 – specificity) was attributed to the large number of true-negative examinations (linked to the low prevalence of disease in the populations studied, which were mostly general populations). The ability of the screener to perform a risk assessment on detected abnormalities equated to the sensitivity of COE. A positive examination in patients with oral mucosal abnormalities showed heterogeneous sensitivity across studies, ranging from 50% (95% CI, 7–93%) to 99% (95% CI, 97–100%); the heterogeneity of the sensitivity prevented pooling of data. Compared with false-positive rates, the higher and heterogeneous overall false-negative rate (1 – sensitivity) was attributed to the relatively small number of patients with true-positive examinations in the general populations studied. The sensitivity and specificity outcomes were based on aggregate data of both oral cancer and OPMDs.

In an attempt to explore the performance of COE to detect oral cancer versus OPMDs, a re-analysis of the data was performed (Walsh et al., 2021b). In four of the data sets, no cancers were detected, and the performance of COE to detect OPMDs ranged from 60% to 81% for sensitivity and from 94% to 99% for specificity (Downer et al., 1995; Ikeda et al., 1995; Jullien et al., 1995). In one large data set in which only cancers were considered positive (i.e. OPMDs were considered negative) (Chang et al., 2011), 3 cancers were missed (i.e. false-negatives) out of

Table 4.1 Performance of COE for detection of oral cancer and OPMDs

Outcome measured	No. screened	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Reference
Oral cancer and OPMDs	2140	59 (39–78)	98 (97–99)	Mehta et al. (1986)
Oral cancer and OPMDs	1872	95 (92–97)	81 (79–83)	Warnakulasuriya and Pindborg (1990)
Oral cancer and OPMDs	3522	97 (96–98)	75 (73–77)	Warnakulasuriya and Nanayakkara (1991)
Oral cancer and OPMDs	2069	94 (90–97)	98 (98–99)	Mathew et al. (1997)
OPMDs	309	71 (44–90)	99 (98–100)	Downer et al. (1995)
OPMDs	985	61 (44–83)	99 (98–100)	Jullien et al. (1995)
OPMDs	1042	81 (64–93)	99 (98–99)	Jullien et al. (1995)
OPMDs	154	60 (32–84)	94 (88–97)	Ikeda et al. (1995)
Oral cancer	13 606	99 (97–100)	99 (99–99)	Chang et al. (2011)
Oral cancer	88	50 (7–93)	98 (92–100)	Sweeny et al. (2011)

CI, confidence interval; COE, conventional oral examination; OPMDs, oral potentially malignant disorders.
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a total of 285 cancers, yielding both sensitivity and specificity of 99%. Four of the data sets comprised both oral cancers and OPMDs (Mehta et al., 1986; Warnakulasuriya and Pindborg, 1990; Warnakulasuriya and Nanayakkara, 1991; Mathew et al., 1997), and among a combined total of more than 9000 people screened, only 1 cancer (out of 36; 2.8%) compared with 95 OPMDs (out of 2309; 4.1%) were falsely identified as screen-negative. [There was no stratification analysis of COE performance by outcome (cancer vs OPMDs). None of the studies specifically assessed whether health workers could adequately discriminate between oral cancers and OPMDs; nonetheless, the high sensitivity and specificity of COE to detect cancer would indicate that such discrimination could be successfully done by trained health workers.]

The overall certainty of the evidence underlying the reported accuracy of COE to detect oral cancer and OPMDs was rated as low (Walsh et al., 2021b).

(c) Mobile technology to improve the performance of COE

Over the past decade, advances in smartphones have enabled their use in health care. A novel approach to oral cancer screening is using mobile phone technology to transmit digital images from the field for specialists to review remotely. Three preliminary studies (two in India and one in Brazil) (Gomes et al., 2017; Birur et al., 2019; Vinayagamoorthy et al., 2019) were included in a recent systematic review exploring the accuracy of remote screening in low-resource settings (Walsh et al., 2021b). In data from 3600 remote screenings, the sensitivity ranged from 82% to 94%, and the specificity ranged from 72% to 100% (Table 4.2), although the overall certainty of the evidence was rated as very low.

Subsequently, Haron et al. (2023) compared the accuracy of COE and the decision to refer (i.e. lesions suspicious for oral cancer or OPMDs) performed on site with those based on clinical images sent via the Mobile Mouth Screening Anywhere (MeMoSA) smartphone application. Non-specialists were trained to capture the digital images. For remote assessment and referral decision, the sensitivity was 94.0% and the specificity was 95.5%.

The feasibility of community health workers using a prototype mobile technology to perform oral cancer screening was evaluated in rural India (Bhatt et al., 2018). The screening process

Table 4.2 Performance of remote screening (with mobile phone technology) for detection of oral cancer and OPMDs

Outcome measured	No. screened	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Reference
Oral cancer and OPMDs	55	82 (57–96)	100 (91–100)	Gomes et al. (2017)
Oral cancer and OPMDs	3414	85 (81–88)	99 (99–100)	Birur et al. (2019)
Oral cancer and OPMDs	131	94 (70–100)	72 (63–80)	Vinayagamoorthy et al. (2019)

CI, confidence interval; OPMDs, oral potentially malignant disorders.
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was well accepted by this high-risk local population, which traditionally had limited access to specialized health-care providers; it also had a positive impact on the social standing of the community health workers using the prototype.

Collectively, these studies have shown opportunities to develop oral cancer screening programmes using technology based on mobile phone photography.

4.1.2 Mouth self-examination

The oral cavity is easily accessible for examination, and most OPMDs and oral cancers are readily visible (see Section 1.3.1), which facilitates mouth self-examination (MSE). Almost 50 years ago, Glass et al. (1975) recommended teaching MSE as part of cancer prevention programmes; after clinical examination, each patient was taught the technique under supervision and encouraged to repeat it every month. Worldwide, MSE is being taught to apparently healthy populations as part of numerous public awareness programmes to promote early detection of oral cancer, particularly in populations at high risk (tobacco smokers and/or alcohol drinkers) (Hussain and Sullivan, 2013; Jornet et al., 2015; Mishra and Bhatt, 2017; Shrestha and Maharjan, 2020).

(a) Description of the technique

To perform MSE, the person stands in front of a mirror under good light to visualize all parts of the oral cavity and the visible parts of the oropharynx. The procedure is a comprehensive examination, which is divided into eight steps: facial symmetry, lips, gingivae, buccal mucosae, tongue and floor of the mouth, palate, oropharynx, and lateral aspect of the neck. This is followed by digital palpation of these structures using the index finger in the same sequence as COE.

The main advantages of MSE are the low cost, the possibility of performing the examination in remote, low-resource areas without diagnostic infrastructure, and increased awareness about oral diseases. The disadvantages are the impact of overdiagnosis of oral diseases, unnecessary referrals, and potential false-negative findings.

(b) Compliance with and performance of MSE for screening

Mathew et al. (1995) were the first to assess the feasibility and performance of MSE in a large trial, in Trivandrum, Kerala, India. About 10 000 copies of a brochure describing risk factors for oral cancer, the appearance of OMPDs and oral cancer, and the method for MSE were distributed to 9000 households by college students in 9 villages over a period of 10 days. In some situations, the students also demonstrated the procedure to the villagers. One week later, a survey

was conducted. Of about 22 000 eligible individuals, only 8028 (36%) had read the brochure and performed MSE, of whom 247 identified an oral lesion and reported to a referral clinic. A benign lesion was diagnosed in 97 cases (39%), and 51 individuals (21%) had normal oral variations. [The accuracy of MSE against clinical diagnosis was not reported.]

Scott et al. (2010) reported the results of a pilot study of diagnostic accuracy of MSE in smokers aged ≥ 45 years who were recruited from a list of general practitioners in south-eastern London, United Kingdom. COE was performed by a dentist in 53 participants and identified OPMDs in 12 participants (22%). Without knowing the results of the dentist's examination, all of the participants received a leaflet on "how to spot mouth cancer early", with details of MSE, and were asked to proceed with self-examination in the room. Most of the participants (39; 74%) found MSE easy to perform. A total of 23 participants (43%) reported noticing one or more lesions. The sensitivity of MSE was 33%, and the specificity was 54%. [The Working Group noted the poor performance of the test, leading to a risk of false reassurance for those with false-negative results and unnecessary anxiety for those with false-positive results.]

Elango et al. (2011) analysed the effectiveness of MSE in coastal villages of Kerala, India, in a high-risk population of 57 704 individuals. A brochure was distributed with information on risk factors for oral cancer and the MSE technique, and instructions to report to an oral cancer screening clinic if any suspicious lesions were identified. Four weeks after the brochure was distributed, trained health workers performed COE on 34 766 available individuals. A total of 30 342 individuals (87%) had practised MSE; 987 (3%) reported not knowing how to perform MSE, 1751 (5%) reported disinterest, and 1580 (5%) did not report any reason. Of the available individuals, 791 (2%) refused to be examined by a health worker. Only 54 individuals identified a suspicious lesion by MSE (of which 39 were confirmed as OPMDs), whereas 219 individuals had a suspicious lesion detected by the health workers. The sensitivity of MSE was 18.0%, and the specificity was 99.9%.

In a study conducted in the Buksa tribal community in Dehradun District (India), out of 539 participants, 220 (40.8%) practised MSE. The prevalence of oral mucosal lesions identified by COE performed by a health worker was 213 (39.5%), whereas only 69 lesions (12.8%) were detected by MSE. The sensitivity was 24.6%, and the specificity was 87.4%. The sensitivity varied from 10.2% for white lesions to 72.7% for ulcers, and the specificity varied from 92.4% for difficulty in mouth opening to 99.3% for red lesions (Shah et al., 2020). In an MSE training programme conducted in this tribal community (Singh et al., 2017), 85 participants attended a health education lecture on MSE and oral cancer. The participants were then asked to perform MSE and report the presence of any abnormalities or oral lesions. Of the 77 study participants who performed MSE, 9 detected a lesion.

The efficacy of MSE was also tested as an alternative to follow-up hospital visits in treated patients with oral cancer (Vaishampayan et al., 2017). MSE is included in the contents of new technologies such as mobile apps for oral cancer awareness (Deshpande et al., 2019).

4.1.3 Adjunctive techniques

An adjunct is defined as a technique or test that if applied in a screening or diagnostic setting would facilitate the detection or assessment of an abnormal lesion. A screening adjunct is not the same as a diagnostic adjunct, and this distinction is important. A screening adjunct is applied to all apparently healthy individuals undergoing oral cancer screening (as part of a population screening programme, or opportunistically to patients attending dental offices) with the sole aim of improving the ability of a screener

to detect disease in a population. A diagnostic adjunct is typically applied only to patients with abnormal mucosal findings after COE, to better characterize such findings and guide clinical decisions.

In the hands of primary care clinicians, the distinction between a screening adjunct and a diagnostic adjunct is subtle. Hypothetical differences might be that occult or small lesions (i.e. disease that is not readily visible during COE) would be more likely to be detected when the technique is used as a screening adjunct (i.e. when COE and the adjunctive technique are used sequentially). In the hands of expert clinicians, such adjunctive techniques might be used in a diagnostic way to facilitate selection of the site of biopsy to aid in mapping or assessing the margins of disease for the purposes of excision. In addition, these techniques might be used in the surveillance setting to monitor patients with OPMDs or with a history of oral cancer who are at risk of malignant development or recurrence (Kerr, 2020).

The adjuncts used in a screening setting are typically point-of-care technologies that provide macroscopic or wide-field information about the entire mouth (i.e. when used as a screening adjunct) or about specific abnormal areas (i.e. when used to examine a lesion or lesions detected by COE) (Kerr, 2020). Table 4.3 compares the utility of adjunctive techniques.

(a) Visualization adjuncts

Visualization or optical adjuncts include devices or machines that expose tissues in vivo to various wavelengths of light, generating optical signals in real time. These adjuncts work on the premise that the optical properties of diseased tissues differ from those of normal tissue (Kerr, 2020).

(i) Tissue autofluorescence

Tissue autofluorescence devices are hand-held and generate violet-blue light (in the 400–450 nm range). This light excites naturally occurring tissue fluorophores, i.e. molecules such as flavin adenine dinucleotide (FAD) and reduced nicotinamide adenine dinucleotide (NADH) in the epithelium and collagen or elastin cross-links in the submucosa. The result is visible fluorescence emission, which enables clinicians to visually scan the mucosa in a darkened environment to detect disruptions in natural tissue autofluorescence (Poh et al., 2010). Two early case series of OPMDs harbouring carcinoma or high-grade dysplasia demonstrated that such lesions exhibited a characteristic loss of fluorescence visualization (fluorescence visualization loss [FVL]), in contrast to normal tissue, which shows normal fluorescence (fluorescence visualization retained [FVR]) (Lane et al., 2006; Poh et al., 2007; Fig. 4.1).

In a single, low-quality study, autofluorescence as a screening adjunct showed no difference compared with COE alone (Simonato et al., 2019). Autofluorescence has been evaluated almost exclusively as a diagnostic adjunct in accuracy studies. A recent meta-analysis of these studies reported a pooled sensitivity of 88% (95% CI, 80–93%) and a pooled specificity of 61% (95% CI, 44–75%) compared with histopathological outcomes, i.e. any grade of oral epithelial dysplasia (OED), carcinoma in situ, or oral squamous cell carcinoma (OSCC) was rated as a positive reference outcome (Table 4.4; Walsh et al., 2021b). The low specificity is attributed to the preponderance of benign lesions that demonstrate FVL (i.e. confounder lesions that yield false-positive outcomes), predominantly inflammatory lesions (such as geographic tongue or erythematous candidiasis), non-inflammatory vascular changes, or pigmented lesions, all of which absorb blue light. Specificity may be increased in primary dental settings through

Table 4.3 Comparison of adjunctive techniques for screening or diagnosis of oral cancer and OPMDs

Technique	Inherent advantages	Inherent disadvantages	Sensitivity	Specificity	Benefits for screening	Disadvantages for screening	Costs for screening	Costs for assessment	Relevance to screening	Current state of development
Autofluorescence	Non-invasive, real-time, hand-held	Requires darkened room; infection-control supplies needed	High	Low	Minimal	Challenging for field population screening; interpretation is challenging for non-experts	Single purchase of device; purchase of infection-control supplies	None, other than time for clinician if used in opportunistic setting	Unclear	Commercially available in some countries
Narrow-band imaging	Non-invasive, real-time	Large, expensive unit; endoscope requires sterilization between patients	High (small number of studies)	High (small number of studies)	Minimal	Impossible for field population screening	Prohibitively high cost for opportunistic screening	None, other than time for clinician if used in opportunistic setting	Not likely	Commercially available in some countries
Tissue reflectance	Non-invasive, real-time, hand-held	Requires darkened room; infection-control supplies needed; requires consumable supplies; requires rinsing steps	High	Very low	None	Interpretation is challenging for non-experts; significant overdiagnosis	Single purchase of device; purchase of infection-control supplies; purchase of rinse	None, other than time for clinician if used in opportunistic setting	Not relevant	Commercially available in some countries
Vital staining	Non-invasive, real-time	Uses consumable supplies; requires rinsing steps; can be messy (stains skin/clothing)	Intermediate	Intermediate	Minimal	Interpretation is challenging for non-experts	Purchase of kits	None, other than time for clinician if used in opportunistic setting	Not likely	Commercially available in some countries, or may be easily prepared from raw materials

Table 4.4 Performance of autofluorescence for detection of oral cancer and OPMDs

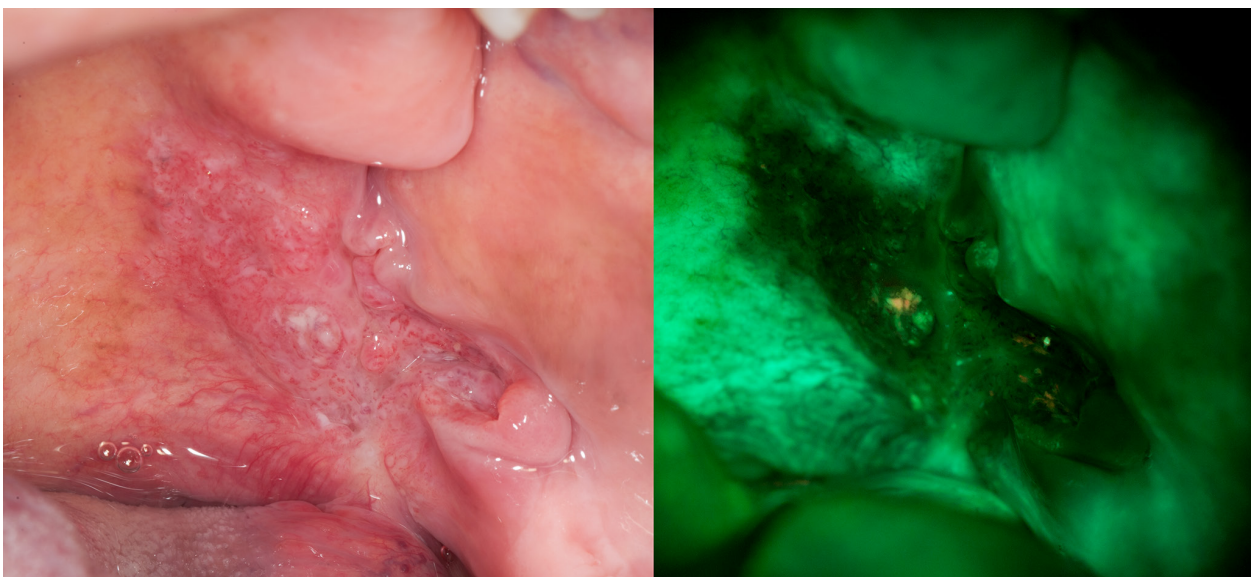
Reference	No. of studies	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Walsh et al. (2021b)	16	2140	OED (any grade), CIS, OSCC	88 (80–93)	61 (44–75)

CI, confidence interval; CIS, carcinoma in situ; OED, oral epithelial dysplasia; OPMDs, oral potentially malignant disorders; OSCC, oral squamous cell carcinoma.

adequate training and/or by reassessing patients with FVL lesions to rule out benign inflammatory lesions (Bhatia et al., 2014; Laronde et al., 2014). False-negative outcomes may occur in patients with dysplastic OPMDs, largely in homogeneous leukoplakias with histopathological evidence of mild OED, but in rare cases even in OSCCs (Truelove et al., 2011). Occult lesions (i.e. lesions not detected by COE) have been detected with autofluorescence, and a small fraction of them harboured OED (Truelove et al., 2011). These results, coupled with the fact that most of the accuracy studies were not generalizable to a primary care dental setting, led an expert panel to recommend against the use of tissue autofluorescence devices by frontline clinicians as screening or diagnostic adjuncts for OPMDs (Lingen et al., 2017a).

One issue that deserves consideration is the mucosal changes associated with chewing of smokeless tobacco or areca nut products. These changes can cause substantial hyper-reflectance (i.e. a bright white signal) as a result of the effect of surface debris on the mucosa (i.e. betel chewers' mucosa), keratosis (such as smokeless tobacco keratosis), or increased collagen deposition (i.e. oral submucous fibrosis). False-positives are also common due to the preponderance of reactive pigmented lesions (i.e. melanosis) in users of smokeless tobacco or areca nut products. Collectively, these findings can make interpretation challenging, and there are no validated

Fig. 4.1 Oral squamous cell carcinoma involving the left retromolar trigone



The image on the left is under white light. The image on the right displays fluorescence visualization loss (FVL).
Courtesy of Alexander Ross Kerr.

Table 4.5 Performance of narrow-band imaging for detection of oral cancer and OPMDs

Reference	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Piazza et al. (2010)	97	Oral and oropharyngeal SCC	96[a]	98[a]
Yang et al. (2013)	317	OED (any grade), CIS, SCC	87 (78–96)	94 (91–97)

CI, confidence interval; CIS, carcinoma in situ; OED, oral epithelial dysplasia; OPMDs, oral potentially malignant disorders; SCC, squamous cell carcinoma.
[a] 95% CI not reported.

objective measures to record or document autofluorescence outcomes.

(ii) Narrow-band imaging

Narrow-band imaging (NBI) is an endoscopic adjunctive technique that is used in the aerodigestive tract to evaluate the surface texture and vascular patterns of the mucosa. NBI units simultaneously emit two distinct narrow bands of light: one in the blue-green range (400–430 nm), which helps delineate superficial vasculature (blood vessels appear brown), and the other in the green range (525–555 nm), which delineates thicker vessels in the submucosa (they appear cyan). The endoscopic NBI unit also facilitates the photographic capture of images. Compared with healthy tissues, OSCC and OED may exhibit abnormal neovascular (angiogenic) patterns; this is the premise for the utility of NBI in the oral cavity.

Based on two studies (Piazza et al., 2010; Yang et al., 2013), the sensitivity and specificity compared with histopathological outcomes (i.e. any grade of OED, carcinoma in situ, or OSCC as a positive reference outcome) ranged from 87% to 96% and from 94% to 98%, respectively (Table 4.5). In both studies, NBI was significantly more accurate than white-light evaluation alone. [The studies were of low quality.]

A commercially available and comparatively inexpensive hand-held multimodal visualization adjunctive device sequentially uses three lights: a white light, a 405 nm violet light to detect autofluorescence, and a 545 nm green light, which is of a similar wavelength to the green light used in NBI. The green light was incorporated into the device to better identify changes in vascularity of OPMDs. Two accuracy studies reported data on the green light compared with histopathological outcomes. They demonstrated low sensitivity and specificity: a sensitivity of 40.0% (95% CI, 24.9–56.7%) and a specificity of 71.0% (95% CI, 63.8–78.0%) (Lalla et al., 2016) and a sensitivity of 78.4% (95% CI, 61.8–90.2%) and a specificity of 15.4% (95% CI, 4.4–34.9%) (Sharma et al., 2021). [The results showed wide heterogeneity, suggesting that this device is not a surrogate for an NBI unit.]

[An NBI unit is a sophisticated and expensive piece of equipment, unlikely to be used for screening by frontline clinicians or in low-resource settings.]

(iii) Tissue reflectance

This diagnostic adjunct was first developed for the evaluation of cervical neoplasia and then adapted for use in the oral cavity (Kerr et al., 2006). The proposed basis for its use in the oral cavity is that OPMDs harbouring OSCC or OED have a differential tissue reflectance compared with normal mucosa. The evaluation of OPMDs is performed in two steps: topical application of an acetic acid solution, followed by direct illumination using a low-wavelength (blue-white) light source. In some of these platforms, the light is generated by a chemical reaction (hence the term "chemiluminescence"), whereas in others the source is a light-emitting diode (LED).

Table 4.6 Performance of tissue reflectance for detection of oral cancer and OPMDs

Reference	No. of studies	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Lingen et al. (2017b)	4	307	Clinically evident, suspicious lesions	81 (71–89)	69 (63–75)
Walsh et al. (2021b)	6	432	OED (any grade), CIS, SCC	94 (35–99)	19 (3–67)

CI, confidence interval; CIS, carcinoma in situ; OED, oral epithelial dysplasia; OPMDs, oral potentially malignant disorders; SCC, squamous cell carcinoma.

A recent meta-analysis of five accuracy studies (Walsh et al., 2021b) yielded poor specificity compared with histopathological outcomes of OED or OSCC, with a pooled sensitivity of 94% (95% CI, 35–99%) and a pooled specificity of 19% (95% CI, 3–67%) (Table 4.6). This technology is currently marketed for use in combination with toluidine blue vital staining. Based on four studies, the combined use of these two adjuncts led to improvements in the pooled sensitivity to 81% (95% CI, 71–89%) and in the pooled specificity to 69% (95% CI, 63–75%) (Lingen et al., 2017b). The studies were considered to have serious issues of risk of bias and indirectness of evidence, which downgraded the quality level of the evidence to very low.

Collectively, these findings led an expert panel to recommend against the use of tissue reflectance devices by general dentists (Lingen et al., 2017a).

(b) Vital staining

Vital staining involves the topical application of a dye to the entire oral mucosa as a screening adjunct, or more commonly as a diagnostic adjunct to assess abnormal mucosal lesions. Most of the research on vital staining is related to the use of toluidine blue and Lugol's iodine.

(i) Toluidine blue

The use of toluidine blue vital staining as a diagnostic adjunct for assessing OPMDs was first reported more than 50 years ago by Niebel and Chomet (1964). The mechanism of action of toluidine blue remains unclear, but it is probably related to its affinity for nuclear material in the context of increased cellular permeability in OSCC and high-grade OED. Toluidine blue stain may be prepared as a 1% or 2% solution or is available commercially in pre-prepared packages or bottles. It is used in conjunction with a 1% acetic acid solution; acetic acid is applied first, followed by toluidine blue, and then acetic acid again (Kerr, 2020). A positive test is commensurate with dark blue staining (Fig. 4.2).

Toluidine blue was tested as a screening adjunct in a community-based randomized controlled trial (RCT) in 7975 people at high risk for oral cancer. Those identified as test-positive (i.e. with positive toluidine blue staining) had a 21% lower incidence rate of OSCC at 5 years compared with the control group (COE only); this result was not statistically significant (Su et al., 2010). In a later systematic review, this study was judged to have high concerns regarding applicability, due to patient selection, and unclear risk of differential verification bias related to the use of a national cancer registry as a reference standard (Walsh et al., 2013).

Most of the literature available for toluidine blue is about its use as a diagnostic adjunct. A recent meta-analysis of 20 accuracy studies, predominantly using toluidine blue as a single stain, reported a pooled sensitivity of 86% (95% CI, 79–90%) and a pooled specificity of 68% (95% CI, 58–77%) compared with histopathological end-points (i.e. any grade of OED or OSCC); the certainty of the evidence was rated as low to very low (Table 4.7; Walsh et al., 2021b). There was broad heterogeneity in accuracy, which may be

Table 4.7 Performance of vital staining for detection of oral cancer and OPMDs

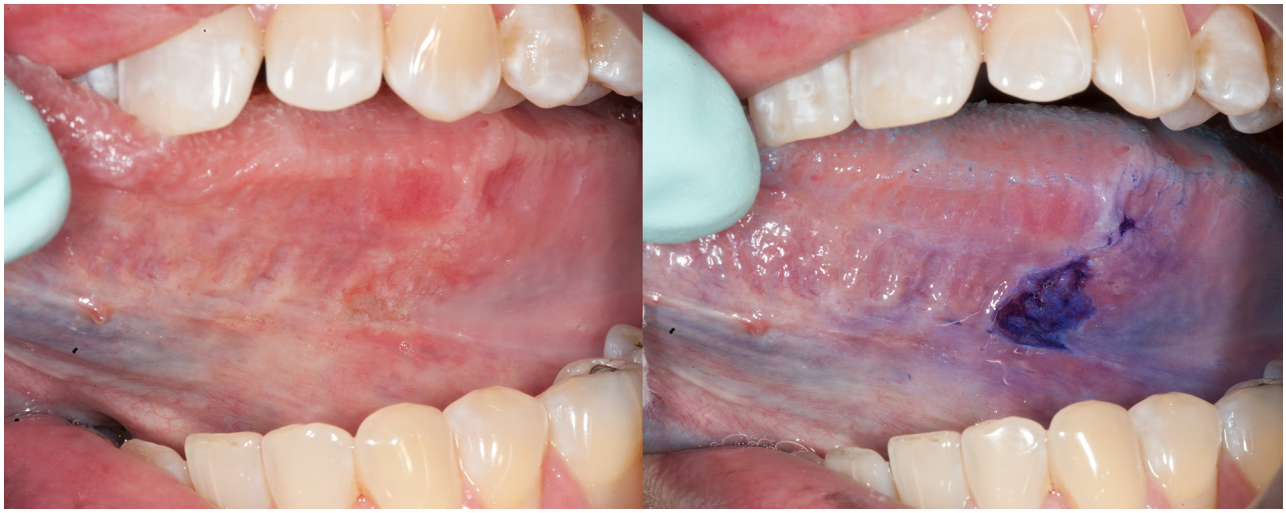
Reference	No. of studies	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Walsh et al. (2021b)	21	1780	OED (any grade), CIS, SCC	86 (79–90)	68 (58–77)

CI, confidence interval; CIS, carcinoma in situ; OED, oral epithelial dysplasia; OPMDs, oral potentially malignant disorders; SCC, squamous cell carcinoma.

attributed to several factors, including the diversity of OPMDs tested (i.e. a higher percentage of high-grade OED, carcinoma in situ, or OSCC will lead to higher sensitivity) (Chainani-Wu et al., 2015) and variability both in the testing protocols and in the interpretation of light or equivocal staining patterns.

Vital staining has potential for both false-positives and false-negatives, and the clinician's experience is critical. False-positives may occur because toluidine binds to benign inflammatory, ulcerative, or regenerating tissues. In addition, the dye may be mechanically retained in the crevices of rough or fissured lesions and the filiform papillae. False-negatives may be due to the inability of the dye to penetrate through thick hyperkeratotic lesions (e.g. homogeneous leukoplakia). In most of the study populations, there is a lower ratio of traumatic and inflammatory oral lesions to OPMDs or OSCCs than would be expected in a general population. Given that primary care clinicians and healthcare workers will encounter a blend of mucosal abnormalities that reflects the general population, even higher false-positive and false-negative rates may be anticipated. Training in the use of toluidine blue may reduce the number of false-positive and false-negative outcomes (Li et al., 2019), and a follow-up visit for repeated staining after allowing sufficient time for traumatic and inflammatory lesions to resolve has long been recommended to improve specificity (Mashberg, 1980).

Fig. 4.2 Oral squamous cell carcinoma involving the left lateral border of the tongue



The image on the left is under white light. The image on the right displays positive toluidine blue staining (royal blue). Note the small satellite of blue staining superiorly.
Courtesy of Alexander Ross Kerr.

Collectively, these findings led an expert panel to recommend against the use of vital staining as a diagnostic adjunct for OPMDs by general dentists (Lingen et al., 2017a).

(ii) Lugol's iodine and other vital stains

Lugol's iodine, named after the French physician Lugol, stains for glycogen content. Therefore, normal non-keratinized oral mucosa will preferentially retain the stain.

Given the contrasting staining effects of Lugol's iodine and toluidine blue, the two agents have been tested in combination to improve the specificity of toluidine blue staining in diagnostic accuracy studies for oral cancer and OPMDs (Epstein et al., 1992; Nagaraju et al., 2010; Chaudhari et al., 2013).

A few other vital stains, such as methylene blue and rose bengal, have a similar staining profile and performance to toluidine blue (Chen et al., 2007; Du et al., 2007).

4.1.4 Cytology and quantitative DNA cytometry

(a) Cytology

The use of cytology was introduced by Papanicolaou and Traut (1943) to detect cervical cancer. Since the 1950s, exfoliative cytology and then brush biopsy cytology were increasingly used as practical, low-risk, and low-cost diagnostic tools for the initial evaluation of OPMDs and oral cancer (Silverman, 1959; Sciubba, 1999; Böcking et al., 2011; Koch et al., 2011; Nanayakkara et al., 2016).

Oral cavity samples are collected with a wooden or metallic spatula (scrape biopsy or exfoliative biopsy), a curette, or a cytological brush (cytobrush biopsy), which is rubbed or scraped (in the case of a spatula) or rotated (in the case of the cytobrush) on the surface of the lesion and then spread onto a glass slide for analysis. Exfoliative cytology collects only superficial cells, whereas cytobrushes can collect superficial, intermediate, and even basal cells (i.e. transepithelial sampling). The malignant or benign nature of the oral lesion is usually evaluated with computer-assisted analysis (Sciubba, 1999; Acha et al., 2005). Epithelial cells collected with a wooden or metallic spatula are usually scarce and can exhibit nuclear and cytoplasmic distortion (Ogden et al., 1992). Cytobrushes improve the capacity to harvest oral mucosa cells and the quality of smears. Although transepithelial sampling can cause some discomfort to the patient, the brush must penetrate deeper (indicated by pinpoint bleeding) in order to collect basal cell layers. This is necessary because dysplastic and early invasive cancer cells are first detected in the basal cell layer (Acha et al., 2005).

Usually, slides are immediately fixed with 95% ethyl alcohol (96° GL), which enables further staining with routine staining methods, such as Papanicolaou, haematoxylin and eosin (H&E), periodic acid–Schiff (PAS), or Feulgen techniques, among others (Pérez-de-Oliveira et al., 2020).

Subsequent laboratory processing methods include simple centrifugation, cytocentrifuge preparation, or cell blocks. The cytocentrifuge approach, which was developed to overcome the issues of insufficient material when using simple centrifugation, enables better results in processing specimens. Fresh samples are collected in anticoagulant vials, loaded into an automated cytospin machine, and centrifuged. Slides containing smears prepared by the cytospin technique are then fixed in 95% ethyl alcohol for 20–30 minutes and stained with H&E, Papanicolaou, or PAS techniques (Qamar et al., 2018). A modified Papanicolaou staining procedure can be carried out in clinical settings that require faster decision-making processes (Thakur and Guttikonda, 2017).

In liquid-based cytology, the cytobrush-collected specimen is placed into a vial containing preservative fluid before transportation to the

laboratory where the specimen is processed, i.e. with cytospin and staining (modified Papanicolaou, or Feulgen in the case of DNA ploidy; see below) or for flow cytometry (Hutchinson et al., 1994; Khandelwal and Solomon, 2010; Olms et al., 2018). In the CDx system, the cytology results are reported as positive (for dysplasia or carcinoma), atypical (cellular changes of uncertain diagnosis), negative (normal cells), or inappropriate (incomplete sample) (Sciubba, 1999; Mehrotra et al., 2011; Nanayakkara et al., 2016). In other reporting systems, the categories may be different.

Cytology with exfoliative biopsy yields high false-negative rates (up to 31%) (Folsom et al., 1972). Modified liquid-based cytology with brush biopsy improves the diagnostic accuracy of cytology for OPMDs and oral cancer (Delavarian et al., 2010; Navone et al., 2011; Deuerling et al., 2019). When the preparation methods of conventional cytology (transfer procedure to glass slides) and liquid-based cytology are compared, liquid-based preparations show a more uniform distribution and less cellular overlapping, cellular deformation, mucus, microbial colonies, and debris compared with those of conventional cytology (Olms et al., 2018). Liquid-based platforms also have technical advantages, including (i) enabling immediate fixation of cells while removing unwanted harvested material (e.g. mucus and debris), (ii) producing thin layers with a clear background and producing more homogeneous samples than conventional smears, and (iii) reducing the proportion of unsatisfactory samples (Hayama et al., 2005; Deuerling et al., 2019); however, the higher cost can be a substantial problem in low-resource settings.

The exfoliative and brush biopsy techniques were compared in a prospective study of patients with leukoplakia (116 lesions) and lesions with a suspicion of malignancy (76 lesions) (Nanayakkara et al., 2016). When only positive results were considered ["high-risk" lesions defined as smears with any degree of dysplasia or malignant cells], compared with histopathological end-points of OSCC, the brush technique had a sensitivity of 89.6% and a specificity of 100%, and the exfoliative technique had a sensitivity of 60.4% and a specificity of 95.2%. When the histopathological end-points included moderate dysplasia or worse, the accuracy increased.

Recent reviews of the performance of cytology for detection of oral cancer and OPMDs are presented in Table 4.8. In a review and meta-analysis of 16 studies (Lingen et al., 2017b), cytology in patients with OPMDs had the highest accuracy among all reviewed adjuncts, with a sensitivity of 92% (95% CI, 86–98%) and a specificity of 94% (95% CI, 88–99%).

A recent review of 24 data sets compared the accuracy of cytology when using a cytobrush (n = 16) or scraping (n = 3) to harvest cells. The overall sensitivity was 90% (95% CI, 82–94%), and the specificity was 94% (95% CI, 88–97%). For cytobrush, the sensitivity was 91% (95% CI, 81–96%) and the specificity was 94% (95% CI, 87–97%); for scraping, the sensitivity was 93% (95% CI, 87–96%) and the specificity was 92% (95% CI, 81–97%) (Walsh et al., 2021a).

Table 4.8 Performance of cytology for detection of oral cancer and OPMDs

Reference	No. of studies (data sets)	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Lingen et al. (2017b)	16	2148	Clinically evident, suspicious lesions	92 (86–98)	94 (88–99)
Walsh et al. (2021a)	24	1950	Oral cancer and OPMDs	90 (82–94)	94 (88–97)

CI, confidence interval; OPMDs, oral potentially malignant disorders.

Table 4.9 Performance of DNA cytometry for detection of oral cancer and OPMDs

Reference	No. of patients	No. of lesions	Outcome measured	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Maraki et al. (2004)	98	98	Oral cancer	100[a]	97.4[a]
Ng et al. (2012)	171	199	Oral cancer and OPMDs	89.3[a]	96.5[a]
Walsh et al. (2021a)[b]	216	525	Oral cancer and OPMDs	76 (68–82)	98 (72–99)

CI, confidence interval; OPMDs, oral potentially malignant disorders.
[a] 95% CI not reported.
[b] Meta-analysis with 5 studies.

In a prospective trial, Sciubba (1999) analysed the accuracy of brush biopsy with computer-assisted sample analysis. Of the 298 cases with lesions judged to be clinically suspicious that underwent brush and scalpel biopsy [excisional biopsy], 102 were malignant. The sensitivity of brush biopsy was 100%, and the specificity was 100% for positive results [definitive cellular evidence of epithelial dysplasia or carcinoma] and 92.9% for atypical results [abnormal epithelial changes of uncertain diagnostic significance].

To evaluate the feasibility of oral brush biopsy in resource-constrained settings, Mehrotra et al. (2008) evaluated 94 patients with OPMDs or oral cancer using a baby toothbrush followed by scalpel biopsy, and the specimens were analysed without computer-assisted analysis. The specimens were adequate in 74 cases, with a sensitivity of 76.8% and a specificity of 93.3%.

Experts from the American Dental Association recommend the use of cytology as a triage tool in primary care settings or if the patient refuses a tissue biopsy (Lingen et al., 2017a).

(b) Quantitative DNA cytometry

DNA cytometry, which is used to detect the cytometric equivalent of chromosomal aneuploidy, was developed as an adjunctive technique to improve the accuracy of cytology. Aneuploidy is defined as an alteration of the chromosome number that is not a multiple of the haploid complement (Williams and Amon, 2009). Because aneuploidy is frequent in cancer cells, DNA cytometry has been used in the context of early diagnosis of oral cancer and OPMDs (Tong et al., 2009).

A recent review included 24 data sets, of which 5 used DNA cytometry. The pooled sensitivity was 76% (95% CI, 68–82%), and the pooled specificity was 98% (95% CI, 72–99%) (Walsh et al., 2021a) (Table 4.9).

In a series of 98 cytobrush and scalpel biopsies of clinically evident lesions, 75 samples were cytologically and histologically negative (the cut-off for true positive was severe dysplasia or carcinoma). The remaining 23 samples, which had positive (15 cases), suspicious (4 cases), or doubtful (4 cases) cytological results, underwent DNA cytometry, and 19 of the 23 cases showed aneuploidy (a sensitivity of 100% and a specificity of 97.4%) (Maraki et al., 2004).

In a retrospective review of 171 patients with 199 suspicious oral lesions who underwent biopsy and quantitative cytology, 28 patients had OPMDs with OED or OSCC, of whom 25 had positive quantitative cytology. False-positive quantitative cytology was observed in 5 of the 143 patients with negative histology; the sensitivity was 89.3%, and the specificity was 96.5% (Ng et al., 2012).

4.1.5 Liquid biopsy

Liquid biopsy is a non-invasive, convenient, and low-cost method, and it is easy to collect liquid samples (Mali and Dahivelkar, 2021). Tumour DNA was detected in 100% of

saliva samples from patients with oral cancer, suggesting that saliva is preferentially enriched with tumour DNA from tumours at this site (Wang et al., 2015). The diagnostic and prognostic applications of "salivaomics" (Wong, 2012) for oral cancer have been extensively explored, with the identification of many potential biomarkers: minerals, peptides, proteins, DNA, messenger RNA (mRNA), microRNA (miRNA), long coding RNA, oxidative stress-related molecules, glucocorticoids, glycosylation-related molecules, telomerase activity, and the microbiome (Li et al., 2004; Jou et al., 2011; Cheng et al., 2014; Yu et al., 2016; Amer et al., 2017; Kaczor-Urbanowicz et al., 2017; van Ginkel et al., 2017; Payne et al., 2018, 2019; Chen and Zhao, 2019; Rapado-González et al., 2019; Hofmann et al., 2020). However, saliva testing has not yet been incorporated into commercial products or clinical practice (Masthan et al., 2012; Walsh et al., 2021a).

The role of cytokines and other proteins as promising salivary biomarkers for oral cancer has been shown consistently in numerous studies. In a large study that included five cohorts (169 cases and 226 controls), interleukin 8 (IL-8) and SAT mRNA had the highest predictive values (Elashoff et al., 2012). In a single study, the combination of the three biomarkers IL-8, SAT, and H3F3A increased the sensitivity and specificity to predict the presence of oral cancer compared with each of the biomarkers separately (Li et al., 2004).

In one systematic review, high sensitivity and specificity were observed for IL-8, choline, pipecolinic acid, L-phenylalanine, and S-carboxymethyl-L-cysteine; however, the combination of different biomarkers did not improve sensitivity or specificity (Guerra et al., 2015). In another systematic review, the proteins found most frequently were IL-8, CD44, matrix metalloproteinase-1 (MMP-1), and MMP-3 (Gualtero and Suarez Castillo, 2016). Recent systematic reviews and a meta-analysis showed that numerous cytokines, such as IL-6, IL-8, and tumour necrosis factor α (TNF-α), are present at significantly higher concentrations in the saliva of patients with oral cancer compared with that of healthy people (Rezaei et al., 2019; Ferrari et al., 2021). Another systematic review also identified IL-8 mRNA as a potential candidate (Gaba et al., 2021).

The most recent systematic review of salivary diagnostic biomarkers for oral cancer and OPMDs, which included 295 articles (Piyarathne et al., 2021), included proteomic biomarkers, cytokines, growth factors, angiogenic factors, antigens, cytokeratin, cell surface receptors, enzymes, and silencing of tumour suppressor genes via promoter hypermethylation. From the reported data, IL-1β, IL-6, and IL-8 were selected as the most suitable salivary biomarkers for early detection of OSCC and OPMDs. [Most of the studies were graded with fair quality and moderate risk of bias.]

Matrix metalloproteinases are also promising saliva biomarkers. Stott-Miller et al. (2011) observed that the concentrations of MMP-1 and MMP-3 were higher in later stages of oral cancer compared with controls, cases with dysplasia, and early-stage tumours, with an area under the curve (AUC) of the receiver operating characteristic (ROC) curve of 0.845 for MMP-1 and 0.877 for MMP-3. Chang et al. (2020) also identified MMP-1 as the most promising candidate from a panel of proteins, with a sensitivity of 76.6% and a specificity of 86.8%. In a systematic review, Hema Shree et al. (2019) observed a high sensitivity for MMP-9 (95%; 95% CI, 88–100%) and chemerin (100%; 95% CI, 78–100%), with a specificity of 100% for both MMP-9 and chemerin. In a systematic review of six studies (with a total of 775 participants), high performance rates were reported for MMP-9 and for CYFRA 21-1 (Gualtero and Suarez Castillo, 2016; AlAli et al., 2020).

Several reviews and meta-analyses have highlighted the diagnostic accuracy of miRNAs in differentiating patients with oral cancer from

healthy controls (Tian et al., 2015; Arantes et al., 2018; Al Rawi et al., 2021; Liu et al., 2021). The most recent meta-analysis, which included 1106 patients and 732 controls, found a pooled sensitivity of salivary miRNAs of 70%, a pooled specificity of 82%, and an AUC of 0.80 (Liu et al., 2021). A previous meta-analysis based on 23 studies found a pooled sensitivity of 75.9%, a pooled specificity of 77.3%, and an AUC of 0.83 (Tian et al., 2015). Among a panel of miRNAs in saliva samples from patients with head and neck cancer (comprising cancers of the oral cavity, oropharynx, larynx, and pharynx) and from healthy controls, miR-9, miR-191, and miR-154 had excellent discriminatory power, with an AUC of 0.85, 0.74, and 0.98, respectively (Salazar et al., 2014). Momen-Heravi et al. (2014) performed a genome-wide evaluation of miRNA patterns in saliva samples from patients with oral cancer, patients with oral lichen planus, and healthy controls and observed that miR-27b had a sensitivity of 85.7% and a specificity of 100% for detection of oral cancer (AUC, 0.96; 95% CI, 0.88–1.05).

Aberrant methylation of tumour suppressor genes is an important epigenetic mechanism of carcinogenesis. Several genes have been found to be more frequently hypermethylated in saliva samples from patients with oral cancer than in those from controls (Carvalho et al., 2008; Arantes et al., 2018; Rapado-González et al., 2021a, b). In a meta-analysis of 18 studies, the frequency of methylation was higher in patients with head and neck cancer (comprising mostly cancers of the oral cavity) than in healthy controls (odds ratio, 8.34; 95% CI, 6.10–11.39); a significant association between methylation of specific tumour-related genes and risk of head and neck cancer [not otherwise specified] was observed for *p16*, *MGMT*, *DAPK*, *TIMP3*, and *RASSF1A* (Rapado-González et al., 2021b).

Finally, changes in the microbiome have been associated with risk of oral cancer (Perera et al., 2016). In dysplastic leukoplakia, the most enriched species were *Fusobacterium*, *Leptotrichia*, *Campylobacter*, and *Rothia* species; severe dysplasia was associated with specific microbial enrichments (*Leptotrichia* spp. and *Campylobacter concisus*) (Amer et al., 2017).

[Despite the great potential of saliva biomarkers in the diagnosis of OPMDs and oral cancers, and the rapidly evolving knowledge in the field and the consistently high accuracy of some of the biomarkers in a research setting, there is a lack of clinical validation regarding this approach in oral cancer screening settings.]

4.1.6 Use of emerging technologies in the primary screening setting

(a) Artificial intelligence for identification of OPMDs

Artificial intelligence (AI) is defined as the process by which a computer is able to learn by continuously incorporating new data into an existing statistical model (Deo, 2015). A promising new approach to improve the detection and diagnosis of OPMDs is to engage the interest of mathematicians with expertise in AI or machine learning to apply these techniques to improve the clinical diagnosis of oral cancer and OPMDs (Kar et al., 2020; García-Pola et al., 2021).

Several groups have investigated the use of AI to improve the efficacy of COE (García-Pola et al., 2021; Ilhan et al., 2021), and the preliminary findings have been promising.

(b) Optical coherence tomography

Optical coherence tomography (OCT) is an optical technology that uses back scattered signals from different layers of tissue to construct in vivo cross-sectional images of tissue with high resolution (Huang et al., 1991; Machoy et al., 2017). This technology is similar to that used in ultrasound, but whereas ultrasound uses sonic signals to generate tissue images, OCT uses optical signals.

OCT has been used for many years for the evaluation and diagnosis of retinal lesions (Fujimoto, 2003). Wilder-Smith et al. (2009) evaluated the use of OCT for diagnosis of oral cancer and OPMDs in 50 patients and found strong agreement between the diagnosis based on OCT images and that based on histology. Heidari et al. (2019) developed a portable OCT system and used it to evaluate oral lesions in 20 patients and 10 healthy individuals. Whereas previous studies had compared the qualitative evaluation of OCT images and histological images, in this small study the researchers developed an objective algorithm to differentiate between normal and abnormal oral mucosa based on the OCT images. They reported a sensitivity and specificity of this algorithm for differentiating between healthy and cancerous or dysplastic mucosa of 95% and 100%, respectively, and a sensitivity and specificity for differentiating between cancer and dysplasia of 91% and 100%, respectively.

James et al. (2021) provided validation of a point-of-care OCT diagnostic device based on an automated algorithm, which was used to examine 232 individuals across a spectrum ranging from normal mucosa to OPMDs and oral cancer. The process included first imaging the lesion and then providing the image to the algorithm for further interpretation. The algorithm score was compared with standard histopathological diagnoses if biopsy was indicated. The algorithm score was unable to distinguish between the grades of dysplasia, but it accurately differentiated oral cancers (OSCC, with a sensitivity of 93%) and OPMDs (with a sensitivity of 95%) from benign lesions and normal mucosa. To provide the delineation of high-grade dysplastic lesions (moderate or severe dysplasia) from low-grade lesions (mild dysplasia, benign, or normal), the research team implemented the use of an artificial neural network, which reached a sensitivity of 83% (James et al., 2021).

(c) In vivo microscopy

Whereas OCT provides a cross-sectional image of the oral mucosa and submucosa, reflectance microscopy and fluorescence microscopy provide images of the oral mucosal surface (Muldoon et al., 2012). Emerging reflectance microscopy technologies, including those that can analyse vascular patterns in the oral submucosa, are adequate to visualize oral tissue without use of contrast agents. However, most fluorescence microscopy approaches require the use of an optical contrast agent, either applied topically or administered intravenously.

Muldoon et al. (2012) described a new high-resolution optical microscopy (high-resolution microendoscope [HRME]), fluorescence microscope (Yang et al., 2018b), which could provide real-time images of the nuclear morphology of the oral mucosa. To enable visualization of the nuclei, topical application of the fluorescent dye proflavine was required. The images obtained could be saved for further analysis of the size and shape of the nuclei by an automated computer algorithm (Yang et al., 2018b). Autofluorescence (see Section 4.1.3) has low specificity for identifying benign lesions. To boost the specificity, a multimodal approach was suggested of merging autofluorescence with HRME technology (Yang et al., 2018b). Subsequent studies that used the HRME instrument, alone and in combination with wide-field autofluorescence imaging devices, have documented the ability of this technology to objectively identify abnormal and dysplastic mucosa with high sensitivity and specificity (Yang et al., 2018a, 2019, 2020). However, this HRME technology is not yet available for clinical use.

Nathan et al. (2014) reported on a preliminary study of 21 participants with oral cancer or OPMDs, who underwent imaging of lesions with confocal laser endomicroscopy for in vivo evaluation of the oral mucosa before resection or excisional biopsy. To provide optical contrast,

the participants underwent intravenous injection of fluorescein before imaging. Qualitative analysis of the images by experts familiar with this technology was compared with histological diagnosis. The overall sensitivity was 80% for diagnosis of dysplasia versus non-dysplasia. Despite these initial positive findings, this technology has not yet been adopted for clinical evaluation of patients with oral mucosal lesions, possibly due to the need for intravenous injection of fluorescein before imaging.

(d) Spectroscopy

In contrast to optical imaging technologies such as OCT and microscopy, optical spectroscopy involves the objective detection and analysis of optical signals collected after tissue is exposed to light of various wavelengths. Basically, clinical spectroscopy is the analysis of how light interacts with tissue (Sahu and Krishna, 2017). Alterations in spectroscopic signals can be used to detect biochemical and architectural changes in oral tissue that are associated with neoplastic progression (Müller et al., 2003; Bigio and Bown, 2004). Several different types of spectroscopic analysis have been evaluated for use in the detection of oral cancer, including Raman spectroscopy, fluorescence spectroscopy, reflectance spectroscopy, elastic scattering spectroscopy, and time-resolved autofluorescence spectroscopy. The distinction between these spectroscopic technologies is based on multiple factors, including the type of light illumination delivered to the tissue and the type of optical signal detected after this illumination (Sahu and Krishna, 2017). These differences arise as a result of how light interacts with tissue. For example, fluorescence spectroscopy involves illumination of tissue at wavelengths that are known to stimulate autofluorescence by tissue components such as collagen, and collection of the autofluorescence light emitted from the illuminated tissue at specific wavelengths (Romano et al., 2021). Reflectance spectroscopy involves assessment of the light reflected from tissue.

Although the reflected light is usually the same wavelength as the illumination light source, in rare cases light is reflected at a different wavelength, due to inelastic scattering (Bigio and Bown, 2004; Sahu and Krishna, 2017). These inelastic reflectance signals, which are often called Raman signals, are very faint compared with fluorescence and standard reflectance signals. However, spectroscopic analysis of Raman signals can provide objective documentation of chemical changes in biological tissues (Bigio and Bown, 2004; Sahu and Krishna, 2017). Raman spectroscopy is a technology that enables non-invasive, molecular interrogation of the chemical composition of biological tissues, using optical interrogation. Four biological components contribute to Raman signals: nucleic acids, lipids, proteins, and water (Bigio and Bown, 2004). Several studies have investigated the potential efficacy of Raman spectroscopy to discriminate between oral cancer or OPMDs and benign or normal oral mucosa. These studies refer to the possible use of this technology both ex vivo, with the use of formalin-embedded tissues (Ibrahim et al., 2021) and biopsies (Matthies et al., 2021), and in vivo, with possible clinical use indicating a potential novel adjunctive diagnostic technique (Sahu et al., 2012).

In contrast, elastic scattering spectroscopy relies on gradients in the optical index of refraction after the light is scattered by specific organelles inside the cell (e.g. nuclei or mitochondria). This spectroscopic method depends on the differences in the densities of the organelles; the elastic scattering spectrum may change in cells undergoing carcinogenesis (Bigio and Bown, 2004).

Fluorescence and reflectance spectroscopy technologies have been used to evaluate oral mucosal lesions in vivo (Schwarz et al., 2008; Messadi et al., 2014). Although these preliminary studies have shown promise for the ability of these technologies to discriminate between normal or benign oral tissue and dysplastic or

cancerous oral tissue, they showed insufficient sensitivity and specificity.

(e) Molecularly targeted optical imaging agents

Given that the standard COE and radiographic imaging are insufficient to determine the extent of OSCC in many patients, several molecularly targeted optical imaging agents have been developed over the past decades to improve the surgeon's ability to delineate the anatomical extent of malignant tissue and high-grade dysplastic disease, before or during surgical resection (Fakurnejad et al., 2019; van Keulen et al., 2019; Steinkamp et al., 2021).

[Although these clinical trials may offer new techniques to improve surgical resection of oral cancer, it is unclear how these molecularly targeted optical imaging agents might improve the early detection and diagnosis of oral precancer and cancer in individuals at high risk, particularly in low-resource settings.]

4.2 Organized and opportunistic oral cancer screening activities

Worldwide, there are very few large-scale population-based organized or non-organized oral cancer screening programmes, and there is very little sporadic screening activity. This is despite the fact that most patients with oral cancer present in advanced stages with poor prognosis. Previous reviews of oral cancer screening have concluded that there is "insufficient evidence to recommend inclusion or exclusion of oral cancer screening" in the general population, and that opportunistic screening of populations at high risk might be effective and should be considered (Hawkins et al., 1999; Kujan et al., 2005; Brocklehurst et al., 2013).

A large-scale population-based oral cancer screening programme in people aged ≥ 15 years has been under way in Cuba since 1982. The programme requires that dentists provide oral visual inspection annually in community dental clinics and refer suspicious cases to the regional head and neck and maxillofacial surgical service for further management. A formal evaluation of the programme for the period 1984–1990 was carried out in collaboration with IARC (Fernández Garrote et al., 1995). The programme covered 12–26% of the target population annually, and less than 30% of the individuals with suspicious lesions complied with referral to the maxillofacial surgical service. The programme identified about 16% of the 4412 incident oral cancers in Cuba during 1984–1990. After the formal evaluation of the programme, the age threshold for the target group was increased to ≥ 35 years as part of reorganization efforts (González, 2014). No further formal evaluation of the reorganized programme has been done since 1995.

A nationwide population-based oral cancer screening programme, which conducts oral visual inspection every 2 years, has been running in Taiwan (China) since 2004. It targets residents aged ≥ 30 years with a history of cigarette smoking and/or betel quid chewing, and Indigenous people aged ≥ 18 years. In 2004–2009, about 55% of invited individuals (n = 4.2 million) participated in screening (Chuang et al., 2017). More than 4.6 million individuals with the exposure of betel quid chewing and/or cigarette smoking have attended the biennial oral cancer screening. A nationwide online information system for breast cancer, colorectal cancer, and oral cancer screening was successfully developed to support health professionals and health decision-makers for planning, delivery, management, and evaluation in the population-based cancer screening programme (Lin, 2018).

India accounts for the largest contribution to the burden of oral cancer globally (Ferlay et al., 2020). Although the Government of India has issued guidelines for oral cancer screening

for all individuals in the age group 30–65 years (National Health Mission of India, 2021), these have yet to be implemented systematically on a large scale and have mostly resulted in sporadic screening. The draft national oral health policy released in February 2021 by the Ministry of Health and Family Welfare of India (Ministry of Health and Family Welfare, 2021) also emphasizes the need for screening, but it provides no clear direction or roadmap on how to achieve this. The Government of Tamil Nadu State in India has organized an oral cancer screening programme since 2016 through public health services. This programme targets people aged ≥ 18 years who are users of tobacco and/or alcohol (National Health Mission Tamil Nadu, 2021). It is supported by an information system, but no data have yet been published from this programme. In an opportunistic oral cancer screening activity, 1 061 088 people in 265 272 houses were surveyed in Kannur District, Kerala, India (Philip et al., 2018).

Sporadic oral cancer screening involving small numbers of individuals has been conducted both in India and in Sri Lanka, demonstrating the feasibility of MSE and/or home-based screening by community health workers, but such activities do not resemble sustained programmatic efforts (Amarasinghe et al., 2016; Philip et al., 2018; Basu et al., 2019). Guidelines have been developed by the National Cancer Control Programme of Sri Lanka for oral cancer screening and management of oral lesions, targeting users of tobacco and areca nut (National Cancer Control Programme, 2020); however, these have not resulted in a sustained programmatic activity.

There has been very little oral cancer screening activity in Central and South America. Since 2001, the São Paulo State Health Secretariat has coordinated oral cancer screening with annual COE, combined with the national campaign for influenza immunization of the population aged ≥ 60 years in São Paolo State, Brazil (Almeida et al., 2012). In 2001–2008, 2 229 273 individuals were screened, with an increase in coverage from 4.1% in 2001 to 16% in 2008, a decrease in the percentage of suspicious lesions from 9% in 2005 to 5% in 2008, and a decrease in the rate of confirmed cases of oral cancer per 100 000 examinations from 20.9 in 2001 to 10.4 in 2008.

No population-based oral cancer screening programmes have been reported in Europe, North America, or Oceania.

4.3 Determinants of participation in screening for oral cancer

The World Health Assembly adopted the first resolution related to oral cancer diagnosis in 2007, and the World Health Organization has formally provided guidance for oral health (WHO, 2007, 2013, 2021). Despite this, most countries have not widely adopted or reported oral cancer screening. In addition, the literature on the determinants of participation in oral cancer screening is scarce.

It is critical to identify and monitor the factors that positively and negatively influence cancer screening programmes and their outcomes, in order to facilitate translation of the scientific evidence of benefit to the clinical setting. The predictors of participation in cancer screening, adherence to follow-up screening rounds, and compliance with referrals for diagnosis and treatment are well established in the literature (Solar and Irwin, 2010). They consist of (a) drivers that influence the process at the level of (i) the individual, (ii) health-care providers, (iii) health-care systems, and (iv) health-care policies, and (b) interventions to increase participation in screening (Table 4.10).

Table 4.10 Determinants of participation in screening for oral cancer

Category of determinant	Facilitator	Barrier	Reference	Location
Individual level				
Risk factors				
		Smoking	Talamini et al. (1994)	Italy
	Smoking		Chang et al. (2011)	Taiwan (China)
	Smoking		Ramadas et al. (2008a)	India
	Betel quid chewing		Chang et al. (2011)	Taiwan (China)
	Alcohol consumption		Nagao and Warnakulasuriya (2003)	Japan
	Alcohol consumption		Ramadas et al. (2008a)	India
Age and sex				
	Age (45–54 years)	Age (> 65 years)	Ramadas et al. (2008a)	India
	Age (40–60 years)	Age (< 40 years and > 60 years)	Chang et al. (2011)	Taiwan (China)
	Middle-aged (55–64 years)	Younger and elderly (< 55 years and ≥ 65 years)	Talamini et al. (1994)	Italy
	Elderly women	Young and middle-aged women	Mishra et al (2021)	India
	Female sex		Ramadas et al. (2008a)	India
		Female sex	Talamini et al. (1994)	Italy
Socioeconomic factors				
	Hindu religion		Mishra et al. (2021)	India
	Marathi mother tongue		Mishra et al. (2021)	India
	High secondary school education		Mishra et al. (2021)	India
	Owning mass media devices (television and/or radio)		Ramadas et al. (2008a)	India
	Larger household size		Ramadas et al. (2008a)	India
Medical factors				
		Absence of symptoms	Talamini et al. (1994)	Italy
	Family history of cancer		Mishra et al. (2021)	India
Health-care system level				
		Inadequate patient referral	Warnakulasuriya et al. (1984)	Sri Lanka

4.3.1 Individual level

(a) Risk factors

Populations at high risk (i.e. individuals with risk factors for oral cancer, such as tobacco use, areca nut use, and alcohol consumption) were found to be more likely to adhere to oral cancer referral consultations and procedures, compared with individuals without these risk factors (Nagao and Warnakulasuriya, 2003; Ramadas et al., 2008a; Chang et al., 2011), except in one study (Talamini et al., 1994), in which smoking habits were negatively associated with compliance with referral.

(b) Age and sex

In three studies, middle-aged patients were more likely to comply with screening procedures, compared with elderly patients and younger patients (Talamini et al., 1994; Ramadas et al., 2008a; Chang et al., 2011). In contrast, Mishra et al. (2021) reported that elderly women were more likely to participate in oral cancer screening, followed by younger women and middle-aged women.

Inconsistent findings describe female sex as a positive predictor (Ramadas et al., 2008a) and a negative predictor (Talamini et al., 1994) of participation in oral cancer screening. In the study of Ramadas et al. (2008a), accrual of individuals was based on home visits in India, and the authors argued that their finding may be explained by the fact that in the population evaluated, women are more likely to be at home during home visits than their male partners. [It is not clear whether women are more likely than men to attend screening.]

[Although age and sex were important predictors in the above-mentioned studies (Talamini et al., 1994; Ramadas et al., 2008a; Mishra et al., 2021), these determinants were not consistent within and between the studies; this may be explained by confounders, biases in analysis, and study design.]

(c) Socioeconomic factors

Mishra et al. (2021) evaluated socioeconomic determinants of participation in oral cancer screening by women with current smoking habits or previous smoking habits (for ≥ 3 consecutive years) in an organized population-based screening programme in Mumbai, India. High secondary school education level, Hindu religion, and Marathi mother tongue were all positive factors associated with participation in oral cancer screening. In addition, Ramadas et al. (2008a) identified larger household size and owning mass media devices (television and/or radio) as socioeconomic factors associated with higher participation rates.

(d) Medical factors

In a study of screening for head and neck cancer (including oral cancer), patients with upper aerodigestive tract symptoms (Talamini et al., 1994) or a family history of cancer (Mishra et al., 2021) were more likely to attend screening than those who were asymptomatic.

4.3.2 Health-care provider level

Trained health-care providers are more likely to promote oral cancer screening. For instance, in a study in Ernakulam District, Kerala, India, about 53 basic health workers were trained by dentists to examine the oral cavity of individuals at high risk and recognize suspicious cancerous and precancerous lesions. Within a 1-year period, screening participation of the target population increased to 33.5% (Mehta et al., 1986). In addition, 45% of individuals were correctly referred, with a sensitivity of 59%. Thus, the training of basic health workers specifically for oral cancer screening through active recruitment dramatically changed the participation rate.

4.3.3 Health-care system level

Warnakulasuriya et al. (1984) recognized that in Sri Lanka only 50% of individuals with a suspicious lesion detected by primary health-care workers were re-examined by skilled professionals at the university referral centre. The authors concluded that the low compliance of the community with follow-up at the referral centre may have been due to lack of awareness about oral cancer and the value of the screening programme, and possibly an inadequate understanding between the individuals and the health workers about referral.

4.3.4 Health-care policies

Only a few countries, such as Cuba, India, Malaysia, Sri Lanka, and Taiwan (China), have adopted oral cancer screening on a large scale. However, the determinants of participation have most often not been reported. Overall, the above-mentioned countries promote distinct screening programmes in terms of target population, coverage, design, and framework; these differences pose challenges for harmonization and comparison of data in terms of not only the health impact but also the determinants of participation in screening (Warnakulasuriya et al., 1984; López Cruz et al., 2003; Sankaranarayanan et al., 2013; Moyer et al., 2014).

4.3.5 Strategies to increase participation in oral cancer screening

Studies have reported on various endeavours to increase participation in oral cancer screening, including individual invitations through billboards, radio advertisements, newspaper advertisements, toll-free hotlines, letters, home visits, educational leaflets, and phone calls (Jedele and Ismail, 2010; Pivovar et al., 2017). However studies designed to specifically evaluate the efficacy of these interventions are scarce and have biases.

Pivovar et al. (2017) described an e-health strategy to increase the selection of individuals at high risk, followed by an active home-based invitation to schedule oral cancer screening. Selecting individuals at high risk through an electronic database enabled improved efficiency and reduced the percentage of potential participants to 1.4% of the total population. [The Working Group noted that no comparison arm was provided to evaluate the magnitude of the impact associated with such an intervention. The study was also sex-biased, by excluding women at high risk.]

Jedele and Ismail (2010) conducted a 2-year oral cancer awareness and screening campaign that targeted African-American men aged ≥ 40 years. The number of billboards and radio advertisements was positively correlated with the number of calls received on the campaign's toll-free hotline number. Also, the calls to the toll-free number resulted in scheduled appointments and screening of patients.

4.4 Effectiveness of screening

In 2013, Brocklehurst et al. (2013) conducted the most recent systematic review of RCTs on screening for oral cancer or OPMDs using COE, toluidine blue vital staining, fluorescence imaging, or brush biopsy. Based on the only RCT that met the inclusion criteria (Sankaranarayanan et al., 2000, 2013), they concluded that as an alternative to a national-based screening programme, opportunistic oral cancer screening by visual examination in a population at high risk might be effective in reducing oral cancer mortality.

4.4.1 Preventive effects of screening

To ascertain the effect of screening on oral cancer incidence and/or mortality, a search was performed for experimental and observational studies that used "no screening" as the control group and that reported incidence of advanced

and/or early oral cancer and mortality from oral cancer. The Working Group identified one experimental study, from which the outcomes observed with the longest follow-up were extracted. No current experimental studies targeted at measuring incidence of advanced oral cancer and mortality from oral cancer were identified. In addition, three observational studies reporting the primary end-points for performance of oral cancer screening for the screening and control groups were identified.

(a) Randomized controlled trials

In the Trivandrum Oral Cancer Screening Study, in Kerala, India, healthy residents aged ≥ 35 years from 13 rural administrative units, considered as clusters, were randomized into an intervention arm (n = 7) and a control arm (n = 6) (Sankaranarayanan et al., 2000, 2005, 2013; Ramadas et al., 2003). Eligible individuals were identified through interviews during home visits; they provided information about their demographic characteristics and individual habits related to risk factors for oral cancer (i.e. tobacco use and alcohol consumption). The longest reported follow-up of this trial was 15 years (until December 2010) (Sankaranarayanan et al., 2013; Table 4.11). All intervention health workers were taught about cancer and trained in oral cancer screening. Of the 96 517 eligible individuals in the intervention arm, 25 144 (26.1%) underwent one round of screening, 22 382 (23.2%) underwent two rounds, 22 008 (22.8%) underwent three rounds, and 19 288 (20.0%) underwent four rounds. Eligible individuals in the control arm received routine care in 1996–2005 and were offered screening in 2006–2008, in which 43 992 (46.1%) of 95 356 individuals participated. Participants with positive screening results were referred for further clinical examination by a specialist (either a dentist or an oncologist). Examinations for all invasive oral cancers included both COE and histological investigation.

After four rounds of screening in the intervention arm, there was a statistically non-significant (12%) overall reduction in oral cancer mortality compared with the control arm (Table 4.12). However, in users of tobacco and/or alcohol, per-protocol analysis showed a statistically significant (24%; 95% CI, 3–40%) reduction in oral cancer mortality and a statistically significant (21%; 95% CI, 5–35%) reduction in incidence of advanced oral cancer (clinical stages III and IV). The reduction in both incidence of advanced oral cancer and mortality from oral cancer increased with the number of rounds of screening (Sankaranarayanan et al., 2013). To adjust an imbalance in risk of oral cancer between the two arms in this study, an intention-to-treat analysis was recently performed based on the 9-year follow-up; this analysis demonstrated a 27% reduction in oral cancer mortality due to screening (hazard ratio, 0.73; 95% CI, 0.54–0.98) (Cheung et al., 2021).

[The Kerala trial has multiple limitations, in particular related to a high non-compliance rate in screen-positive individuals, i.e. only 59% of screen-positive individuals complied with the clinical assessment by the physicians. The publication does not describe well whether and how the interval cancers were followed up. The cancers that developed in the non-compliant individuals were included in the no-screening group, which assumes per-protocol analysis instead of intention-to-treat analysis; however, the intention-to-treat analysis performed later reached a similar conclusion. No formal training certificate was issued to the health workers; however, all the health workers underwent an examination at the end of the training to test their skills in completing the questionnaire and also in identifying the relevant lesions in the oral cavity. Those whose performance was poor were retrained. It is possible that the health workers' lack of a certificate was perceived as indicating a low qualification and may have resulted in the low follow-up rate of screen-positive individuals.]

Table 4.11 Description of the cluster-randomized trial of the efficacy of oral cancer screening (Sankaranarayanan et al., 2013)

Location Randomization	No. of participants	Participation rate	Accrual period for screening		Age at entry (years)	Description of the intervention	Follow-up for screen-positive individuals	Follow-up rate for screen-positive individuals	Screening interval (years)	No. of rounds of screening Follow-up (years)
			Invited group	Control group						
Kerala, India Cluster-randomized (at the municipal level)	191 872 recruited; 96 517 in the intervention group; 77% men	Intervention arm (at least one screen): 92%; at first round: 79% Control arm: 46.1%	1996–2008	Routine care in 1996–2005, screened in 2006–2008	≥ 35 Mean, 49 (SD, 0.7)	Clinical oral examination by non-medical health worker	Clinical examination by a specialist (dentist or oncologist)	59%	3	4 15

SD, standard deviation.

Table 4.12 Results of the cluster-randomized trial of the efficacy of oral cancer screening (Sankaranarayanan et al., 2013)

Outcome	Population group	No. of participants (screened/control group)	Outcome per 100 000 person-years (screened/control group)	RR (95% CI)
Incidence of oral cancer				
	General population	895 310/898 280	31.2/27.2	1.14 (0.91–1.44)
	Users of tobacco and/or alcohol	429 620/377 350	59.2/61.6	0.97 (0.79–1.19)
Incidence of stages III and IV oral cancer				
	General population	895 310/898 280	16.4/17.7	0.92 (0.72–1.17)
	Users of tobacco and/or alcohol	429 620/377 350	32.2/40.9	0.79 (0.65–0.95)
Mortality from oral cancer				
	General population	895 310/898 280	15.4/17.1	0.88 (0.69–1.12)
	Users of tobacco and/or alcohol	429 620/377 350	30.0/39.0	0.76 (0.60–0.97)

CI, confidence interval; RR, relative risk.

(b) Observational studies

Two cohort studies, both based on a nationwide population-based biennial oral cancer screening programme in Taiwan (China), and one case–control study, evaluating the national oral cancer screening programme in Cuba, compared oral cancer screening attenders with non-attenders in terms of oral cancer incidence and/or mortality.

A cohort of 4 234 393 adults (≥ 18 years) who smoked cigarettes and/or chewed betel quid underwent biennial oral screening by dentists or physicians in 2004–2009 in Taiwan (China). The individuals were followed up until 2012, with a median follow-up of 4.5 years (Table 4.13; Chuang et al., 2017). Screen-positive individuals were referred to specialists in hospitals for histopathological examinations. The study was linked to the National Cancer Registry to enable precise recording of oral cancer cases in attenders and non-attenders in the screening programme. The expected incidence and mortality rates of non-attenders were estimated based on previous findings that about 90% of oral cancer cases were attributed to cigarette smoking and/or betel quid chewing. The participation rate at the first screening in the invited population was 55.1%. There was a 21% (95% CI, 18–24%) reduction in the incidence of advanced oral cancer and a 26% (95% CI, 23–28%) reduction in oral cancer mortality in the screened group compared with the non-screened group (Table 4.13). [The lower incidence rate of oral cancer in the screened group compared with the non-screened group may be due to an imbalance in risk of oral cancer between attenders and non-attenders, considering the low participation rate.]

[To assess the transferability of the conclusions on effectiveness of oral cancer screening to other settings, the following biases should be considered. First, enrolment of the participants was conducted in communities and in hospitals, with an unclear distribution between these two settings. Enrolment of participants in hospitals is likely to increase selection bias. Selection bias also increases with the retrospective choice of the controls related to the outcome of interest. Second, the participation rate of < 60% means that there is a high risk of non-response bias. Third, because the nationwide oral cancer screening programme in Taiwan (China) included an initial survey on the risk factors, this could potentially lead to contamination of the control group, which would lead to an underestimation of the benefits of screening.] A retrospective analysis of the at-risk cohorts invited to the oral cancer screening programme in Taiwan (China) was subsequently conducted by Ho et al. (2019). The study used the databases of the National Cancer Registry, the Nationwide Oral Mucosal Screening Program, and the National Death Registry. The duration of follow-up was calculated from the date of cancer diagnosis to the date of death or to the end of the follow-up period (until 2017). A total of 18 625 patients with oral cancer were identified from the National Cancer Registry during 2012–2015. The screened status was defined as having no records, records without a previous positive result, or records with a previous positive result. Of this cohort, 8165 patients (43.8%) attended at least one screening round and had a previous positive result, 3560 patients (19.1%) had a negative result on screening or no previous positive result, and 6900 patients (37.0%) had no records of attending the screening. Among the patients with cancer, most of the screened patients were diagnosed with cancer at earlier stages compared with the non-screened patients (Table 4.14). The 3-year survival rates were 71.4% for screened patients with positive results, 68.7% for screened patients with negative results, and 63.5% in the non-screened group; this showed a survival benefit of screening.

[The study of Ho et al. (2019) has several limitations. Although the oral cancer screening programme included individuals aged ≥ 18 years, this study limited the cohort to ages ≥ 30 years.

Table 4.13 Prospective cohort study of the effectiveness of oral cancer screening

Reference Location	Description of the cohort	Description of the controls	Accrual and follow-up periods	Participation rate and follow-up rate for screen-positive individuals	Detection rate	Cancer incidence/ mortality RR (95% CI)	Comments
Chuang et al. (2017) Taiwan (China)	4 234 393 high-risk invitees (cigarette smokers and/or betel quid chewers), followed up until the end of 2012; median follow-up, 4.5 years (National Cancer Registry)	Non-attenders; incidence and mortality rates were adjusted to attribute 90% of cases to a high-risk population; 86% men	10.5 million person-years of follow-up	Participation rate: 55.1% Referral follow-up rate: first screening, 91.1%; subsequent screening, 92.6%	*First screening:* Screen-positive, 18 116 (0.8%) Precancer, 11 051 (0.5%) Cancer, 4110 (0.2%) *Subsequent screening:* Screen-positive, 5825 (1.0%) Precancer, 3782 (0.6%) Cancer, 791 (0.1%)	*Incidence* Cancer: 0.83 (0.81–0.86) Advanced cancer: 0.79 (0.76–0.82) *Mortality* 0.74 (0.72–0.77)[a]	Reports also by age groups. The highest detection rate for men was in the age group 50–69 years and for women was in the age group ≥ 70 years

CI, confidence interval; RR, relative risk.

[a] Adjusted for self-selection bias.

Table 4.14 Retrospective cohort and case–control studies of the effectiveness of oral cancer screening

Reference Location	Description of the cohort/ cases	Description of the controls	Established programme: year of start, screening age, screening interval	Oral cancer or precancer end-point	Proportion of patients with events	Cancer incidence/ mortality RR (95% CI)
Ho et al. (2019) Taiwan (China)	Retrospective cohort of patients with oral cancer (2012–2015); high-risk invitees (cigarette smokers and/or betel quid chewers); 95.4% men	Patients without previous screening records; 82.1% men	Population-based biennial programme since 2004 targeting population aged ≥ 30 years	Early-stage diagnosis Survival Mortality	*Stage 0–I diagnosis:* Screened positive, 34.3% Screened negative, 34.3% Not screened, 27.8% *3-Year survival:* Screened positive, 71.4% Screened negative, 68.7% Not screened, 63.5%	Mortality in 3 years: HR[a]: 0.78 Stage 0–I diagnosis: HR[a]: 1.23
Sankaranarayanan et al. (2002) Cuba	Cases: 200 patients with oral cancer (77% men); median age, 65 years	Controls: 3 per case, matched on age, sex, and residence; 77% men	Population-based annual programme via oral inspection since 1984 in population aged ≥ 15 years; screening is mainly opportunistic	Incidence of advanced cancer	Screened cases: 56.0% Screened controls: 49.7%	Incidence of advanced cancer OR: Adjusted, 0.78 (0.53–1.15) Not adjusted, 0.67 (0.46–0.95)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

[a] Calculated from the probability of having an event in 3 years in the screened positive and not screened groups.

The retrospective design carries a risk of misclassification and information bias. The screened cohorts included only a population at high risk, whereas the proportion of cigarette smokers and/or betel quid chewers among the screening non-attenders was unclear. The higher proportion of women in the non-screened group (17.9%) than in the screened group (4.6%) suggests a risk of bias. The comparison is done between five groups, none of which included the "all screened" population (i.e. with either a positive or a negative screening result). The lower hazard ratio for oral cancer mortality in all the groups in the reported Cox regression analysis (e.g. in those with a confirmed cancer and in those who had a positive screening result but did not complete confirmation of diagnosis) compared with those who were not screened suggests a possible risk of bias.]

A case–control study was conducted to evaluate the effectiveness of the national oral cancer screening programme in Cuba (Sankaranarayanan et al., 2002). The cases were 200 individuals with incident oral cancer of stages III and IV registered in 1994–1997. Three controls of apparently healthy individuals were matched to each case on sex, age (± 5 years), and residence (within a 200 m radius of the household of the case). A total of 462 (77%) males and 138 (23%) females provided data on socioeconomic factors and individual risk factors for oral cancer. The proportion of screened individuals was higher in cases than in controls (56.0% vs 49.7%). The odds ratio for advanced oral cancer in cases screened 3 months before diagnosis was 0.67 (95% CI, 0.46–0.95). After adjustment for the frequency of cigarette smoking to address selection bias, the odds ratio was 0.78 (95% CI, 0.53–1.15) (Table 4.14). A time series analysis compared incidence of early oral cancer and mortality from oral cancer in Cuba in 1983–1990 and concluded that the proportion of stage I cases increased from 24% in 1983 to 49% in 1990, without an impact on mortality rates (Fernández Garrote et al., 1995).

[The Working Group noted that the low coverage of the programme and the poor compliance with referral contribute to selection bias. Given the study design, there is also a possible risk of reporting bias. Another risk is recall bias and differential reporting of exposure in cases and controls due to the timing of the event. Furthermore, the definition of the intervention, which was "any visit to a community dentist", may lead to a possible overestimation of exposure in the controls. Finally, the number of cases may be too small to detect a difference in outcomes with an opportunistic screening programme.]

Several studies have assessed the impact of oral cancer screening on oral cancer incidence (Fernández Garrote et al., 1995; Sankaranarayanan et al., 2013; Chuang et al., 2017; Morikawa et al., 2021). Chuang et al. (2017) reported a statistically significant decrease of 17% in the oral cancer incidence rate. All other studies reported no impact.

4.4.2 Harms of screening

Although screening must by definition be beneficial, it may be associated with some harms. The harms related to screening for cancer at other sites have been reviewed extensively (e.g. Welch and Black, 2010; Woolf and Harris, 2012; Marmot et al., 2013).

The potential harms of screening include factors associated with false-positive tests, false-negative tests, overdiagnosis, and overtreatment. A false-positive test result is a positive test result in an individual who does not have cancer in the further assessment. A false-positive test result can lead to unnecessary psychological distress and anxiety, unnecessary additional investigations to rule out disease, side-effects, unnecessary treatment, and additional costs. A false-negative test result is a negative test result in an individual who has the disease. A

false-negative test leads to false reassurance of not having disease and consequent increased risk of advanced disease, with poor treatment outcome and poor cosmesis and functional outcomes. Overdiagnosis is 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. Although the concept of overdiagnosis is often discussed in the context of screening asymptomatic people, there is no agreement on how to estimate overdiagnosis. Estimates of overdiagnosis are highly heterogeneous and vary depending on the analytical approach. Overall, the harms are worse when the quality of the test is poor.

No studies have reported on harms from the oral cancer screening test itself (COE), from false-positive or false-negative screening test results, or from overdiagnosis. However, several studies have reported the detection rates and screening performance in various oral cancer screening programmes (see Section 4.1.1).

Diagnostic harms are primarily related to the side-effects and complications of biopsy for suspected oral cancer or its potential precursors. Although oral cancer screening can detect OPMDs, it is unclear which OPMDs regress spontaneously and which lesions persist or progress further to malignancy (see Section 1.3.1) (Moyer et al., 2014). The treatment of some screen-detected OPMDs is limited by a field cancerization effect due to the entire oral mucosa being exposed to carcinogens. Moreover, surgical and ablative treatments of OPMDs may lead to unwanted side-effects, such as severe pain, infection, and bleeding due to complications of treatment.

4.5 Risk-based model for screening

Cancer screening has historically been based on age and applied for all eligible individuals without any assessment of their exposure to known risk factors. However, the risk of developing cancer varies among individuals. Restricting screening to only individuals at high risk may improve the efficiency and effectiveness of screening while minimizing the harms. A risk-based screening strategy has been tested in several model-based studies and cohorts (Amarasinghe et al., 2010; Shieh et al., 2017; Cheung et al., 2019; Willoughby et al., 2019; de Koning et al., 2020; Harkness et al., 2020; Ten Haaf et al., 2021). Recently, several studies have reported that incorporating genomic information along with other individual risk factors can help in screening for breast cancer, prostate cancer, and lung cancer (Torkamani et al., 2018; Callender et al., 2019; Roberts et al., 2021).

The Trivandrum Oral Cancer Screening Study showed that the benefit of screening is limited to the individuals at high risk, i.e. those who use tobacco and/or consume alcohol (Sankaranarayanan et al., 2005). A reanalysis of the Trivandrum study using a risk-based screening strategy showed that the absolute benefits of screening increased significantly with increasing model-predicted risk of oral cancer (Cheung et al., 2021). The difference in the oral cancer mortality rate between the intervention arm and the control arm increased from 0.5 per 100 000 in the lowest quartile of oral cancer risk to 13.4 per 100 000 for individuals in the highest quartile. Similarly, among ever-users of tobacco and/or alcohol, the difference in the oral cancer mortality rate between the intervention arm and the control arm increased from 1.0 per 100 000 in the lowest quartile of oral cancer risk to 22.5 per 100 000 for individuals in the highest quartile. In a population similar to that in the Kerala trial, screening of 100% of eligible individuals (ages ≥ 35 years) would lead to a 27.1% reduction in oral cancer mortality at a number needed to screen of 2043. Restricting screening to ever-users of tobacco and/or alcohol with no additional risk stratification (43.4% of the population) would substantially increase efficiency (23.3% reduction in oral cancer mortality at a number needed to screen of 1029). Screening the

50% of ever-users of tobacco and/or alcohol at highest risk based on the risk-prediction model (21.7% of the population) would further enhance efficiency with little loss in programme sensitivity (19.7% reduction in oral cancer mortality at a number needed to screen of 610) (Cheung et al., 2021).

[This study provided the first proof of principle that a risk-based tailored approach may enhance the efficiency of screening, reduce harms, and be more cost-effective. However, the magnitude of risk associated with each risk factor may vary in different populations and countries (see Section 2.1) (Winn et al., 2015). This aspect should be considered before implementing a risk-based approach for a particular country. The risk-based approach may be appropriate for resource-limited countries with a high incidence of oral cancer (Cheung et al., 2021; D'Cruz and Vaish, 2021). However, the implementation of a risk-based screening programme faces several challenges in selecting the high-risk group without negatively influencing the trade-off between individual benefits and harms.]

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5. SUMMARY

5.1 Oral cancer and oral potentially malignant disorders

5.1.1 Anatomy of the oral cavity and the oropharynx

The oral cavity is the entrance to the gastrointestinal tract. It is bounded anteriorly by the lips, posteriorly by the faucial arches anterior to the tonsils, laterally by the cheeks (buccal mucosae), superiorly by the palate, and inferiorly by the muscular floor. The tongue occupies the floor of the oral cavity. The subsites of the oral cavity include the lips (mucosal surface or labial mucosae), oral commissures, buccal mucosae, tongue, gingivae (gums), floor of the mouth, and palate.

The oropharynx is a tube-shaped fibromuscular structure behind the oral cavity, continuous with the nasopharynx superiorly and the hypopharynx inferiorly. It extends from the lower surface of the soft palate to the upper border of the epiglottis and communicates with the oral cavity anteriorly. The palatine tonsils project from the lateral wall of the oropharynx, and the lingual tonsils are found on the posterior third (base) of the tongue.

5.1.2 Global burden

Cancer of the oral cavity is the most common cancer type in the head and neck region of the body, with about 380 000 new cases and 180 000 deaths worldwide in 2020. Cancer of the oropharynx is less common, with an estimated 98 412 new cases and 48 143 deaths worldwide in 2020. The estimated age-standardized incidence rates of oral cancer are highest in Melanesia and South Asia. The incidence rate of oropharyngeal cancer is highest in Europe. The incidence rate of oral cancer is highest in countries with medium levels of the Human Development Index, and the incidence rate of oropharyngeal cancer is highest in countries with very high levels of the Human Development Index; low socioeconomic status is associated with an increased risk of both cancer types. During the past two decades, the observed incidence rates of oral cancers have generally decreased, especially in North America, some countries in South-East Asia, and some countries in Europe. The incidence rates of oropharyngeal cancer appear to be increasing in most countries worldwide. Because of population growth, the burden of oral cancer and oropharyngeal cancer will increase in the next two decades.

5.1.3 Oral neoplasia

(a) Classification and natural history of OPMDs and oral cancer

An oral potentially malignant disorder (OPMD) is defined as any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer. OPMDs include leukoplakia, proliferative verrucous leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus, oral lichenoid lesions, oral graft-versus-host disease, oral lupus erythematosus, actinic keratosis, palatal lesions in reverse smokers, and dyskeratosis congenita. OPMDs are a heterogeneous group of lesions, and the transformation rates to cancer vary from 1.4% to 49.5%; the presence of epithelial dysplasia is the most significant predictor. The highest-risk OPMDs are proliferative verrucous leukoplakia and erythroplakia, and the risk is lowest for oral lichen planus. The natural history of OPMDs is not always linear or predictable. They may persist unchanged, progress towards cancer, or even regress.

The clinical features of OPMDs vary according to the type of OPMD. The clinical features of oral cancer vary depending on the site and the stage of presentation. Early cancers may present as erythroleukoplakic lesions with red, white, or mixed red and white areas. As the disease advances, there is ulceration and/or nodularity (exophytic or endophytic tumours). Prognosis of oral cancer depends on multiple factors, including tumour-, host-, and treatment-related factors. Spread of cancer to the regional lymph nodes has a direct negative effect on prognosis.

(b) Stage at diagnosis and stage-related survival

Stage at diagnosis is one of the main factors that affects cancer prognosis. Most patients with cancers of the oral cavity are diagnosed with advanced disease. Besides staging, access to health-care systems, associated comorbidities, and the quality of treatment planning also affect the prognosis. The 5-year survival rate of oral cancer ranges from 0% to 64% across countries, with a median of 39%. The Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system (eighth edition) has recently been updated to enable improved staging and prediction of prognosis of patients with oral cancer.

(c) Treatment and management of OPMDs and oral cancer

OPMDs are a clinically diverse group of disorders, which require a careful clinicopathological evaluation and monitoring over long periods, and their clinical management is challenging. Consensus guidelines for clinical management of patients with leukoplakia or erythroplakia, oral submucous fibrosis, and oral lichen planus have recently been proposed. After clinical identification, the current reference standard is to perform a biopsy for histopathological diagnosis, treatment guidance, and prognostication based on the grade of epithelial dysplasia. Preventive strategies (modifying known risk factors) can reduce risk of oral cancer. Both topical or systemic agents and surgical excision or ablation of OPMDs have been proposed. No consensus exists about time intervals of serial follow-up, which remains important for monitoring and surveillance.

Management and treatment of oral cancer are multidisciplinary. Treatment pillars include combinations of surgery, chemotherapy, radiotherapy, and, more recently, immunotherapy, for early-stage and locally advanced disease.

5.2 Reducing incidence of cancer or precancer

5.2.1 Established risk factors

Tobacco smoking, alcohol consumption, smokeless tobacco use, chewing areca nut products (including betel quid) [hereafter referred to as "areca nut"] with or without tobacco, and infection with human papillomavirus type 16 (HPV16) are classified by the International Agency for Research on Cancer (IARC) *Monographs* programme as carcinogenic to humans (Group 1) and are established risk factors for cancers of the oral cavity. Tobacco smoking, alcohol consumption, and chewing areca nut with tobacco are also established risk factors for pharyngeal cancer. HPV16 infection is an established cause of oropharyngeal cancer.

(a) Tobacco smoking

In most countries, tobacco smoking is the leading cause of oral cancer and oral cancer death. The risk of oral cancer increases with increasing frequency (number of cigarettes smoked per day), duration (in years), and cumulative pack-years of smoking. The duration of smoking has a stronger effect on risk of oral cancer than the frequency of smoking does, but the elevated risk becomes significant at a low number of cigarettes smoked per day. For a given level of exposure, the risk of oral cancer conferred by tobacco smoking is similar by sex. Cigar, pipe, and bidi smoking are associated with a significantly increased risk of oral cancer. Tobacco smoking also causes oropharyngeal cancer, with a dose–response increase in risk. Worldwide, about one quarter to one third of oral cancers and 30–49% of oropharyngeal cancers are attributable to tobacco smoking alone. The main OPMDs caused by tobacco smoking are leukoplakia and erythroplakia.

(b) Alcohol consumption

Consumption of alcohol, particularly heavy alcohol consumption, is associated with an increased risk of oral cancer and oropharyngeal cancer. For the same cumulative exposure, higher alcohol intake for shorter duration confers a greater risk of oral cancer compared with lower alcohol intake for longer duration. Alcohol consumption also confers an elevated risk of OPMDs, particularly leukoplakia. Alcohol consumption increases synergistically in combination with tobacco smoking and accounts for 64% of the population attributable risk of oral cancer.

(c) Smokeless tobacco use

Use of smokeless tobacco (products containing tobacco but not including areca nut or betel quid) increases the risk of oral cancer in a dose-dependent manner with increasing frequency of use (times per day), duration of use (in months), and amount of time the product is retained in the mouth. The risk of oral cancer, after accounting for concurrent smoking, appears to be higher in women than in men. The fraction of oral cancers attributable to smokeless tobacco use is high (50–68%) in countries in South and South-East Asia and in the Sudan, and is much lower (1.6–6.6%) in North America. Smokeless tobacco use increases the risk of OPMDs, particularly leukoplakia.

(d) Chewing areca nut products (including betel quid) with added tobacco

Chewers of areca nut with added tobacco are at increased risk of oral cancer and oropharyngeal cancer compared with never-chewers. The effect is larger in women than in men. The risk of oral cancer increases with frequency (times per day) and duration (in years) of chewing. Chewers of areca nut with added tobacco also have increased risk of OPMDs compared with never-chewers, and the risk is highest for oral

submucous fibrosis, erythroplakia, and leukoplakia. The risk of OPMDs increases with the frequency of chewing (times per day), the duration of chewing (in years), and a younger age at the start of chewing. In India, the population attributable fraction of chewing betel quid with added tobacco for oral cancer was estimated to be higher in women (63.2%) than in men (44.7%). The population attributable risk for OPMDs was estimated to be 84% in Sri Lanka.

(e) Chewing areca nut products (including betel quid) without tobacco

Chewing areca nut without tobacco is predominant in Taiwan (China) but also occurs in other countries in South-East Asia, including Bangladesh, India, Myanmar, Sri Lanka, and Thailand. Chewers of areca nut without tobacco are at increased risk of oral cancer compared with never-chewers. The risk of oral cancer increases with the frequency (times per day) and the duration of chewing. Chewers of areca nut without tobacco also have increased risk of OPMDs compared with never-chewers; the highest risks have been reported for oral submucous fibrosis, erythroplakia, and leukoplakia. The risk of OPMDs increases with the frequency of chewing (times per day), the duration of chewing (in years), and a younger age at the start of chewing. In Taiwan (China), the population attributable fraction of chewing areca nut without tobacco was estimated to be 57.3% for oral cancer, 85.4% for oral submucous fibrosis, and 73.2% for leukoplakia.

(f) HPV16 infection

HPV infections are acquired primarily through sexual activity. HPV16 infection is associated with a < 5-fold increased risk of oral cancer and with a 14-fold to > 100-fold increased risk of oropharyngeal cancer. HPV16 infection causes ~2% of oral cancers worldwide. In contrast, there is wide geographical heterogeneity in attributable fractions of HPV for oropharyngeal cancers, ranging from about 40–50% in North America, Europe, Australia and New Zealand, Japan, and the Republic of Korea to < 15% in most other parts of the world. This heterogeneity may arise from a combination of differences in relevant sexual behaviours and the prevalence of exposure to other risk factors.

(g) Combined effects of established risk factors

Combined exposure to more than one of the risk factors confers a risk that is the sum of the individual risks for each of these carcinogens, and can confer a risk that exceeds the sum or the multiplication product of the individual risk estimates.

The relative risk of oral cancer in individuals who both smoke tobacco and consume alcohol is greater than multiplicative (i.e. the joint effect is greater than the multiplication product of the individual effects). The relative risk of oral cancer in individuals who smoke tobacco, consume alcohol, and chew areca nut with or without tobacco is greater than additive (i.e. the joint effect is greater than the sum of the individual effects).

(h) Additional potential risk factors

Other potential risk factors for oral cancer include second-hand smoke, indoor air pollution, low socioeconomic status (measured by education level, income, occupation), chronic mechanical irritation, and drinking hot maté. Other potential risk factors are dysbiosis of the oral microbiome; exogenous environmental, occupational, and infectious exposures; and poor oral hygiene or oral health, resulting in persistent or chronic inflammation.

5.2.2 Impact upon quitting

(a) Tobacco smoking

Since the *IARC Handbooks* Volume 11 evaluation (in 2006), two cohort studies, one meta-analysis of 17 case–control studies (including

3302 cases of oral cancer and 16 377 controls), and two additional case–control studies on incident oral cancer consistently showed a progressive reduction in the relative risk of oral cancer with increasing time since quitting smoking, with a statistically significant trend in four of these studies. The reduction in risk was evident in all studies within 10 years of smoking cessation. In the meta-analysis, the risk of oral cancer became significantly lower in former smokers compared with current smokers within 4 years after cessation (35% reduction), and the estimated relative risk in former smokers reached the relative risk in never-smokers after ≥ 20 years of smoking cessation, based on fully adjusted risk estimates taking into account frequency of alcohol consumption and cumulative smoking.

The body of evidence on oral cancer and smoking cessation included populations with a wide geographical distribution across North America, Central and South America, Europe, and Asia, including both men and women in four of five studies. The reported risk estimates were based mostly on former and current smokers of cigarettes but also included a minority of smokers of other tobacco products (cigars, pipes, and hand-rolled cigarettes).

Based on a single study that combined oral cancer and pharyngeal cancer, quitting smoking at any age was associated with a significant reduction in the risk of these cancers compared with current smokers, with a progressive and significant lowering of the risk with decreasing age at quitting.

Nine studies on smoking cessation and incidence or prevalence of OPMDs were identified, conducted in Brazil, India, Kenya, Puerto Rico, Sri Lanka, Taiwan (China), and the USA. In a large cohort study in India comparing former versus current bidi smokers after 10 years of follow-up, the incidence of leukoplakia decreased substantially (85% decrease) after smoking cessation. In addition, a large community-based case–control study nested within an intervention study in India reported a 70% increase in risk of leukoplakia in former smokers compared with never-smokers, in contrast to a > 3-fold increase in risk in current smokers. In case–control studies, estimates of the relative risk in former smokers compared with never-smokers ranged from 0.5 to 4.9; the 95% confidence interval often included 1, and the magnitude was mostly, but not always, markedly lower than the relative risk in current smokers (which ranged from 0.48 to 10.0).

(b) Alcohol consumption

Four studies were identified that reported estimates of the relative risk of oral cancer by time since cessation of alcohol consumption: one pooled analysis of case–control studies and three other, smaller case–control studies. In addition, two cohort studies were identified that had data on former alcohol drinkers relative to never-drinkers. The large international meta-analysis from 2010, which pooled data on 3302 cases of oral cancer from 13 case–control studies, found that the reduction in risk of oral cancer after alcohol cessation increases with time since cessation; the effects were more pronounced in former heavy drinkers (≥ 3 drinks per day), reducing the risk by > 50% by 20 years of quitting (odds ratio, 0.43; 95% confidence interval [CI], 0.28–0.67) for oral cancer, and were less clear for oropharyngeal and hypopharyngeal cancers combined. Of the three earlier smaller informative case–control studies, only the one in India reported data comparing former versus current drinkers, and found a tendency for reduction in the risk of oral cancer associated with ≥ 10 years of quitting (odds ratio, 0.62; 95% CI, 0.19–2.05).

No studies on the impact of duration of alcohol cessation on risk of OPMDs were identified. Based on data from seven case–control studies, risk estimates for OPMDs in former drinkers relative to never-drinkers were generally higher than for current drinkers relative to

never-drinkers, particularly for leukoplakia and erythroplakia.

(c) Smokeless tobacco use

A total of six studies were available that examined the association between former use compared with never use of smokeless tobacco and risk of oral cancer. (None of the studies considered current users of smokeless tobacco as the reference group, and none provided risk estimates by time since quitting use.) There were two large cohort studies, in Sweden and Norway, and four case–control studies, three in Sweden and one in Yemen. Neither of the two cohort studies found an association between use of oral snuff (former use or current use) and risk of oral cancer; they reported non-significant relative risk estimates for former users of 0.7–1.0. Although both cohort studies were well powered, exposure categories for smokeless tobacco use (as current, former, and never use) were defined at study entry only, with no reassessment of status of snuff use. In addition, neither of the studies adjusted for alcohol consumption. These limitations are particularly important given the long follow-up period of 12–35 years. The registry-based case–control study in Sweden, which included 128 cases of oral cancer and 756 matched controls, reported a 1.8-fold non-statistically significant increased risk of oral cancer in former oral snuff users after adjustment for potential confounding factors.

Data from eight studies on the association between former use of smokeless tobacco and risk of OPMDs were inconsistent, and all except one study lacked a definition of former users with regard to duration of cessation.

(d) Chewing areca nut products (including betel quid) with added tobacco

Evidence for reduction in risk of oral cancers or OPMDs with cessation of chewing areca nut with added tobacco comes from five published studies (three cohort studies and two case–control studies, all in India), one published meta-analysis, and two primary analyses undertaken by the Working Group (one cohort study and one case–control study, both in India). A primary intervention study in India assessed only OPMDs (leukoplakia) as the primary outcome.

Results from the published studies were inconsistent. Three out of five studies reported a non-significantly lower relative risk of oral cancer in former chewers compared with that in current chewers. The other two studies reported an increased risk, but the estimates were not adjusted for tobacco smoking and alcohol consumption, and the results could be due to reverse causation. Results from the meta-analysis did not show any inverse association. Nevertheless, primary analyses from the cohort study in India showed a reduction in risk of oral cancer in former chewers of 3% (95% CI, 1–4%) per year of cessation of chewing areca nut with added tobacco. In addition, results were consistent across studies for a reduction in the relative risk of OPMDs by duration of cessation of chewing areca nut with added tobacco. The primary prevention study showed strong reductions in the incidence of leukoplakia 5 years after the intervention, by 49% (95% CI, 7–72%) in men and 81% (95% CI, 70–89%) in women.

(e) Chewing areca nut products (including betel quid) without tobacco

Evidence for reduction in risk of oral cancers or OPMDs with cessation of chewing areca nut without tobacco comes from four published case–control studies (three in Taiwan [China] and one in Papua New Guinea), one published meta-analysis, and four primary analyses undertaken by the Working Group (three cohort studies and one case–control study, all in Taiwan [China]). Cessation of chewing areca nut without tobacco was consistently associated with a reduction in the relative risk of oral cancer in former chewers compared with current chewers; the inverse association was significant after long-term cessation

(≥ 15 years of quitting). Based on the primary data analyses, risk reductions per year of cessation ranged from 2.3% to 6.7%. Furthermore, risk reductions were generally larger for younger ages at cessation. In addition, results were consistent across studies for a reduction in the relative risk of OPMDs in former chewers compared with current chewers, and by duration of cessation of chewing areca nut without tobacco.

(f) HPV16 infection

Three types of vaccines against HPV infection are currently available: a bivalent vaccine, a quadrivalent vaccine, and a nonavalent vaccine. All three target HPV16, the type that causes most HPV-associated oral and oropharyngeal cancers. HPV vaccines are prophylactic (i.e. vaccination prevents future acquisition of infection) and not therapeutic (i.e. vaccination does not enable clearance of prevalent infection). Studies show strong evidence of reduction in the prevalence of oral and oropharyngeal HPV16 infection in vaccinated individuals compared with unvaccinated individuals. Because HPV vaccines were only approved recently (in 2006 for women and in 2011 for men in most countries worldwide), the impact of HPV vaccination will take several years or even decades to result in a reduction in incidence of oral cancer or oropharyngeal cancer. However, the anticipated reductions in the incidence of HPV-associated oral cancer and oropharyngeal cancer will depend on the extent of vaccination coverage in the population in any specific country.

5.2.3 Preventive dietary agents

Several studies have examined the protective effects of consuming coffee, tea, fruits and vegetables, and dietary fibre on the incidence of oral cancer. Several population studies have shown a significant inverse relationship between coffee intake and incidence of oral cancer. The effect of tea intake is unclear, with some studies showing a non-significant protective effect and others showing no benefit; it should also be noted that drinking very hot beverages (at temperatures > 65 °C) may increase risks of oral cancer and pharyngeal cancer. Studies examining consumption of fruits and vegetables found a general reduction in the relative risk of oral cancer associated with increasing consumption of fruits or vegetables. Consumption of dietary fibre has also been shown to have protective effects on development of oral cancer.

The effects of dietary agents on the development of OPMDs were examined in several population-based studies conducted in India and Sri Lanka, and a hospital-based study in Italy. In general, consumption of foods and nutrients rich in dietary fibre, vitamins A, C, E, and B12, β-carotene, lycopene, folate, retinol, α-tocopherol, and antioxidant mineral zinc has been found to be protective against the development of OPMDs. Also, biochemical studies were conducted on serum or plasma samples from patients with leukoplakia or oral submucous fibrosis. The available data indicate that the consumption of foods and nutrients rich in certain vitamins and antioxidants may inhibit the development of OPMDs.

5.3 Cessation of smokeless tobacco and/or areca nut use

5.3.1 Product definition and description

The term "smokeless tobacco" refers to a large variety of commercially available or non-commercially available products that contain tobacco as the principal constituent and that are used either orally (chewing, sucking, placing in the cheek or lip pouch, or drinking) or nasally, without combustion. Areca nut is the seed of *Areca catechu* L. and is used as a chewing substance, either alone or in combination with other substances. Areca nut is the primary component of betel quid, which may also be

consumed without tobacco. Smokeless tobacco and areca nut may be consumed separately or combined.

Smokeless tobacco or areca nut products are available as a myriad of products. The products vary substantially in their names and their use in each region; the greatest diversity is observed in South and South-East Asia.

Both smokeless tobacco and areca nut contain multiple carcinogens, and both have been classified as carcinogenic to humans (Group 1) by the *IARC Monographs* programme.

5.3.2 Prevalence of consumption

(a) WHO South-East Asia Region

The World Health Organization (WHO) South-East Asia Region has the highest prevalence of use of areca nut and smokeless tobacco products in adults worldwide, ranging from 2.1% in Thailand to 27.5% in Bangladesh. In 2019–2020, about 30% of men and about 13% of women in India were daily users of smokeless tobacco or areca nut products. In several countries (e.g. Bangladesh, Indonesia, and Thailand), the prevalence of use is higher in women than in men. The prevalence of use of smokeless tobacco or areca nut products is also high in young people in this region; Nepal has the highest reported prevalence in adolescents (16%). South-East Asia is culturally very diverse, and the forms in which these products are prepared and mixed are highly variable. Therefore, it is generally not possible to disaggregate data for areca nut and for smokeless tobacco. Commonly used products include *gutka*, *khaini*, *gul*, betel quid (with or without tobacco), and *supari*.

(b) WHO Western Pacific Region

The WHO Western Pacific Region is culturally extremely diverse. Consumption of areca nut is common in Hunan Province (China) and in Taiwan (China), where the prevalence of use is about 10% in men, but the prevalence is decreasing in older people. Use of areca nut and betel quid has spread from the Philippines across the Western Pacific islands over the past century; the prevalence of use is about 80% in Palau and the Solomon Islands. Smokeless tobacco use is not common. Initiation of use of areca nut products by young people is increasing, for example in Guam (USA).

(c) WHO European Region

In the WHO European Region, the overall prevalence of use of both areca nut and smokeless tobacco is low, with a prevalence of use in most countries of less than 2%. However, in four countries the prevalence exceeded the global average for smokeless tobacco use (6%). There is a marked use of specific types of smokeless tobacco (*snus*) by men, in Nordic countries and in populations in central Asia; also, people of Asian descent and immigrants from South Asia may have use patterns from those regions. The prevalence of use was highest in Sweden (14%) and Norway (18%), with a higher prevalence of use in men than in women. Areca nut, *gutka*, and *zarda* are imported and are used only by immigrant communities from Bangladesh, India, and Pakistan, in which a prevalence of use of about 7% is reported.

(d) WHO Region of the Americas

In the WHO Region of the Americas, the use of smokeless tobacco and areca nut is not culturally embedded, and only limited data are available about patterns of use in the general population. A relatively small spectrum of smokeless tobacco products (e.g. snuff, *snus*, *iqmik*, *chimó*, plug) is currently used by about 1.4% of the population (ranging from 0.2% in Argentina to 3.5% in Venezuela), with a higher prevalence of use in men (2.5%) than in women (0.3%). Several factors are involved in the prevalence of smokeless tobacco use in this region, such as immigrants from South Asia, military personnel, baseball players, middle and high

school students, and the *quilombola* community. Areca nut is not commonly used in this region, except in scattered populations in Hawaii (USA).

(e) WHO African Region

The WHO African Region has the second-highest prevalence of smokeless tobacco use in adults worldwide, with an estimated 15 million adult users. Most users of smokeless tobacco are men (8 million), but the prevalence of use in women is high in some countries. The prevalence of smokeless tobacco use ranges from 0.1% in women in Eritrea to 25% in men in Madagascar. Smokeless tobacco is commonly used without areca nut, through nasal or oral application. Some of the commonly used products are *shammah* (moist snuff), *taaba* (snuff), and *paraky*. Use of areca nut without tobacco by a minority population of South Asian descent has been reported in some countries (e.g. South Africa).

(f) WHO Eastern Mediterranean Region

In the WHO Eastern Mediterranean Region, there are about 21 million adult users of smokeless tobacco. The prevalence of use is much higher in men (~18 million) than in women (~3 million). The prevalence of use and the products used vary across countries. The most common smokeless tobacco products used in the region are *toombak* (especially in the Sudan) and *naswar* (a similar product that is common in the Arabian Peninsula). The prevalence of smokeless tobacco use ranges from 0.1% in women in Egypt to 34% in men in Afghanistan.

(g) Determinants of use

Determinants of use of smokeless tobacco and areca nut can be categorized into individual, social, and environmental factors.

Among individual factors, users' level of knowledge about the harmful health effects of use is a determinant of use of smokeless tobacco or areca nut. In addition, perceived positive effects such as relieving headaches, improving sleep quality, inducing relaxation, aiding decision-making, reducing boredom, and inducing a feeling of being energized are facilitators for use of smokeless tobacco and areca nut. Use of smokeless tobacco is associated with older age groups, and men generally have a higher likelihood of use.

The socioeconomic determinants of use of smokeless tobacco and areca nut are income level, employment, and education level. A large proportion of users of smokeless tobacco have low socioeconomic status, especially in unemployed people. Type of employment also determines use behaviour. The proportions of users of smokeless tobacco and areca nut are high in occupations that require long working hours or continuously repeated activities, such as in drivers and construction workers. With regard to education level, lower education levels are consistently associated with increased prevalence of smokeless tobacco use. The relatively low cost of the quid compared with smoked tobacco has been reported to be a socioeconomic determinant of areca nut use.

Socioculturally, influence from family members and peer pressure are important determinants of both smokeless tobacco use and areca nut use. Sharing of areca nut is a usual practice during social gatherings and is a significant cultural identifier, which reinforces social acceptance. It is also considered a symbol of love and marriage in many places, notably in India and in Taiwan (China). Sociodemographic factors for smokeless tobacco use include area of residence; there is a higher propensity for smokeless tobacco use in rural areas than in urban areas. Advertisements are another determinant of use of smokeless tobacco and areca nut.

5.3.3 Interventions for cessation of use

(a) Behavioural interventions

Nine intervention studies assessed the effects of behavioural interventions for cessation of use of smokeless tobacco or areca nut products in adults: six randomized controlled trials (RCTs) in the USA, one RCT in Sweden, and two large cohort studies in India. Interventions included dental examination; brief advice by physicians, dentists, or behavioural scientists, together with a written manual or leaflet; audiovisual support; follow-up telephone call; quitline support; and other forms of support. Controls received brief advice as in usual care, a written manual, and/or delayed intervention. Of the nine studies, four RCTs in the USA and the two cohort studies in India showed significant effects on the cessation rates, with relative risk ranging from 1.28 (95% CI, 1.09–1.50) to 25.70 (95% CI, 13.26–49.84) for the intervention arm compared with the control arm. The remaining three RCTs (two in the USA and one in Sweden) did not show significant effects; in addition, the numbers of smokeless tobacco users in both the intervention group and the control group were limited in the RCT in Sweden.

Five intervention studies assessed the effects of behavioural interventions for cessation of use of smokeless tobacco or areca nut products in youth: four RCTs in the USA and one large cohort study in India. Interventions included peer-led components, training by trained group leaders or athletes, further supported with tailored audiovisual meetings at periodic intervals. Controls received either no intervention or delayed intervention, general anti-tobacco education, or the general help of a support group. One RCT in the USA showed significant effects on the cessation rates in the intervention arm compared with the control arm, which received no intervention. The other four studies showed effects that were not statistically significant; of note, three of the studies included some sort of intervention in the control arm. One study reported a significant effect on the prevention of initiation of smokeless tobacco use in some of the participants in the intervention and control arms who were non-users at baseline.

(b) Pharmacological interventions

Three RCTs assessed the effects of pharmacological interventions for cessation of use of smokeless tobacco or areca nut products: two with nicotine replacement therapy (one with nicotine gum in India and one with nicotine lozenge in the USA) and one with antidepressants in Taiwan (China). Compared with the behavioural intervention received by the controls, neither nicotine gum nor nicotine lozenge had an effect on the cessation rates for use of smokeless tobacco and areca nut products. In the third study, use of both antidepressants showed significant effects on cessation rates compared with placebo for use of areca nut products (including betel quid) without tobacco (escitalopram: relative risk, 6.33; 95% CI, 1.53–26.14; moclobemide: relative risk, 6.17; 95% CI, 1.48–25.64 at 2 months).

(c) Combined pharmacological and behavioural interventions

A total of 16 RCTs were reviewed to assess the effects of pharmacological interventions in combination with behavioural interventions for cessation of use of smokeless tobacco or areca nut products. Two studies were on nicotine gum, four on nicotine patch, four on nicotine lozenge, three on bupropion (an antidepressant), and three on varenicline (a nicotinic receptor partial agonist). All of the studies were conducted in the USA, except for two studies on varenicline, of which one study was in Norway and Sweden and one study was in India. The study populations were users of smokeless tobacco alone (in the USA and in Norway and Sweden) or of smokeless tobacco or areca nut with tobacco products (in India). All studies performed intention-to-treat analyses or treated participants who withdrew and/or were

lost to follow-up as non-abstinent. Most studies (13 of 16) had a long follow-up (from 6 months to > 12 months). Nine of the 16 studies had at least 100 participants each in the intervention and control arms. In all studies except one, controls were provided with a combination of placebo plus behavioural therapy. Only two studies showed significant positive effects on cessation rates, one using varenicline (relative risk, 1.42; 95% CI, 1.08–1.79) and one using nicotine lozenge (relative risk, 1.27; 95% CI, 1.10–1.47); in both studies, the control arm also received the behavioural intervention. Most of the other studies showed non-significant positive effects; non-significant negative effects were found in three studies, and no effect was reported in one study.

5.3.4 Policies and their impacts

(a) Control policies for smokeless tobacco

Implementation of the articles of the WHO Framework Convention on Tobacco Control to control smokeless tobacco use is at an intermediate stage in the 182 countries that have acceded to the WHO Framework Convention on Tobacco Control.

Articles 4 and 5: Prevention of initiation of smokeless tobacco use in youth. In two studies in Bihar, India, school-based tobacco control policies showed positive effects in reducing the prevalence of smokeless tobacco use.

Article 6: Price and tax measures on smokeless tobacco. One study in the USA showed that taxation had reduced the prevalence of smokeless tobacco use. Four other studies, three in India and one in Bangladesh, showed that higher taxation would reduce the prevalence of use. A large meta-analysis of studies in five countries showed that a 10% price increase would reduce the demand for smokeless tobacco by 2.1%.

Article 11: Packaging and labelling of smokeless tobacco products. Three studies in India showed that large pictorial warnings on product packages are noticed by users and lead to motivation to quit and thinking about quitting.

Article 12: Education, communication, training, and public awareness on smokeless tobacco. Three studies in India and one study in Bangladesh showed that noticing anti-smokeless tobacco messages in the mass media is associated with intention to quit and attempts to quit.

Article 13: Ban on smokeless tobacco advertising, promotion, and sponsorship (TAPS). One study in India and one in the Sudan showed that restricting point-of-sale advertising near schools has an impact on the prevalence of smokeless tobacco use.

Article 14: Demand reduction measures concerning smokeless tobacco dependence and cessation. In one study in the USA and three studies in India, quitlines reported high cessation rates in the callers.

Article 16: Access to and availability of smokeless tobacco to minors. In Sri Lanka, enforcement of the policy of no sales to minors (aged < 18 years) led to a reduction in the prevalence of smokeless tobacco use by minors, as shown by two successive rounds of the Global Youth Tobacco Survey after this policy was adopted. However, in many places, adoption of a policy of no sales to minors has not been successful.

Bans on smokeless tobacco products. In three studies in India, bans have had some initial effect on prevalence of use. However, online sales and smuggling have been reported in Bhutan, India, Sri Lanka, and some European countries. One study in India showed that in view of the *gutka* ban, former users of *gutka* were turning to alternative, vendor-made mixtures (e.g. *mawa*) containing similar ingredients to *gutka*.

Article 20: Research, surveillance, and exchange of information on smokeless tobacco. In Bangladesh, India, and Thailand, a reduction in smokeless tobacco use was found in the second round of the Global Adult Tobacco

Survey after several control policies were implemented at the same time.

Overall, applying multiple key tobacco control policies simultaneously has an amplifying effect.

(b) Control policies for areca nut products (including betel quid)

Areca nut control policies are slowly emerging in countries where areca nut has traditionally been used. Taiwan (China) is the only country with an areca nut control programme; the prevalence of betel quid use has continued to decrease for more than 10 years.

Only a few countries have more than one policy. Taiwan (China) has the highest number of policies (six policies), followed by Myanmar (four policies) and India (three policies). The most commonly adopted policy is a ban on spitting in public places, as has been implemented in Bhutan, Myanmar, Papua New Guinea, and Taiwan (China), as well as in India (by the railways only) and in Hangzhou City (China).

The policies implemented in Taiwan (China) in 1997 are a ban on spitting in public places, a ban on chewing in certain workplaces and in the military, awareness programmes, a betel quid cessation programme, a plantation programme to help areca nut growers change to other crops, and an oral mucosal screening programme to monitor the effect of the policies. As a result, the prevalence of areca nut use in adults (aged ≥ 18 years) has decreased steadily, from about 45% in 2007 to about 5% in 2017. After having increased over several decades, the annual incidence rate of oral cancer has plateaued at about 42 per 100 000 people since 2009.

5.4 Screening and early diagnosis of oral cancer

5.4.1 Screening methods and technologies

(a) Clinical oral examination

Clinical oral examination is the only screening method for the detection of oral cancer and OPMDs that is routinely used. It consists of a visual inspection of the oral cavity and palpation of the neck to identify enlarged lymph nodes or masses. The specificity of clinical oral examination ranges from 75% to 99%, based on numerous studies conducted in Brazil, India, Japan, Portugal, Sri Lanka, Taiwan (China), and the United Kingdom. In contrast, the sensitivity of clinical oral examination for OPMDs and oral cancer was more heterogeneous across studies, ranging from 50% to 99%. Correct risk stratification of oral mucosal abnormalities detected by clinical oral examination is challenging, given the overlap in the signs and symptoms of OPMDs and oral cancer with those of benign mucosal diseases; therefore, primary screeners should be well trained. A limited number of studies on dental care workers have assessed the efficacy of training programmes. In low-resource settings, community health-care workers can be successfully trained to perform clinical oral examination.

Mobile phone technology platforms for remote screening (i.e. via the transmission of digital images for remote evaluation by an expert clinician) are currently being developed and tested.

(b) Mouth self-examination

The oral cavity is easily accessible for examination, and most OPMDs and oral cancers are readily visible. In mouth self-examination, individuals examine their own oral cavity to identify OPMDs or cancerous lesions. The accuracy of mouth self-examination for detection of OPMDs and early-stage cancer varies, from 8.6%

to 72.7% for sensitivity and from 54% to 99% for specificity; also, compliance with performing mouth self-examination varies from 36% to 88%. Several studies have assessed the detection rate of OPMDs.

(c) Adjunctive techniques

Visualization adjuncts and vital staining are techniques that aim to improve the performance of clinical oral examination to identify and/or risk-stratify patients with OPMDs and oral cancer. These adjuncts are rarely used in primary screening, and most of the evidence on their performance comes from secondary or tertiary care settings, against the reference standard of histopathology.

Visualization adjuncts include tissue autofluorescence, narrow-band imaging, and tissue reflectance. Tissue autofluorescence shows the highest performance, with a pooled sensitivity of 88% (95% CI, 80–93%) and a pooled specificity of 61% (95% CI, 44–75%). The low specificity is attributed to the preponderance of benign lesions, which yield false-positive outcomes. Consumption of smokeless tobacco or areca nut by the patient limits the interpretation of autofluorescence.

Vital staining with toluidine blue or Lugol's iodine involves the topical application of a dye directly to the oral mucosa to detect or highlight abnormal mucosa. A recent meta-analysis of 20 data sets assessing the accuracy of toluidine blue staining reported a pooled sensitivity of 86% (95% CI, 79–90%) and a pooled specificity of 68% (95% CI, 58–77%). The potential for false-positives is high because toluidine blue binds to benign inflammatory, ulcerative, or regenerating tissues. Toluidine blue staining has been tested as an adjunct to clinical oral examination in one screening study, showing a non-significant 21% reduction in cancer incidence.

(d) Cytology and liquid biopsy

Brush biopsy cytology may be used as a practical, low-risk, and low-cost diagnostic adjunct in patients with OPMDs and oral cancer. Brush biopsy showed the highest accuracy among all diagnostic adjuncts compared with histopathological end-points, with a sensitivity of 90% (95% CI, 82–94%) and a specificity of 94% (95% CI, 88–97%).

Liquid biopsy is a minimally invasive diagnostic method that analyses biomarkers in samples of circulating fluids, such as blood or saliva ("salivaomics"). The use of saliva samples in the diagnosis of oral cancer and OPMDs has been extensively explored. Potential salivary biomarkers include minerals, peptides, proteins, DNA, messenger RNA, microRNA, long coding RNA, oxidative stress-related molecules, glucocorticoids, glycosylation-related molecules, telomerase activity, and the microbiome. However, the diagnostic applications of salivaomics have been explored only recently.

(e) Emerging technologies

Artificial intelligence is used in medical diagnostics, and its use has been proposed to improve the detection and diagnosis of OPMDs and to distinguish the oral mucosa at highest risk of malignant transformation from the normal mucosa.

Optical coherence tomography is an optical diagnostic technique used for in vivo imaging of OPMDs. Also, in vivo microscopy can be adapted for the same purpose to provide a cross-sectional image of the oral mucosa: techniques such as reflectance microscopy and fluorescence microscopy provide the possibility of detailed mucosal diagnostics, sometimes with the aid of an optical contrast agent (topical or intravenous). When spectroscopy is used, contrast agents are not needed; instead, the light reflected at the same wavelength (elastic scattering) or different wavelengths (Raman spectroscopy) is measured.

Finally, molecularly targeted optical imaging agents have been developed to delineate the margins of oral cancer; however, it is unclear how they could be used in a screening setting.

5.4.2 Organized and opportunistic oral cancer screening

Worldwide, there are very few large-scale population-based organized or non-organized oral cancer screening programmes, or sporadic screening activities. A large-scale population-based annual oral cancer screening programme has been under way in Cuba since 1982, first targeting individuals aged ≥ 15 years and later those aged ≥ 35 years. A nationwide population-based biennial oral cancer screening programme has been running in Taiwan (China) since 2004, targeting cigarette smokers and/or betel quid chewers aged ≥ 30 years and Indigenous people aged ≥ 18 years; more than 4.6 million people have participated in this screening programme.

In India and Sri Lanka, the governments have issued guidelines for oral cancer screening, but these have yet to be implemented systematically on a large scale. There has been very little oral cancer screening activity in Central and South America. Since 2001, the São Paulo State Health Secretariat has coordinated oral cancer screening with annual clinical oral examination for the population aged ≥ 60 years in São Paulo State, Brazil. No population-based oral cancer screening programmes have been reported in Europe, North America, or Oceania.

5.4.3 Determinants of participation in screening for oral cancer

Few studies have reported determinants of participation in oral cancer screening, with different outcome measurements for participation in screening (screening participation, compliance with referral, and adherence to follow-up visits or screening rounds). Determinants of participation can be identified mainly at three distinct levels: the individual, the health-care provider, and the health-care system. Factors that are positively associated with screening participation and compliance with referral include the presence of symptoms, a family history of cancer, higher education levels, and exposure to risk factors such as tobacco smoking, alcohol consumption, and betel quid chewing. In addition, training of primary health-care workers for oral cancer screening and adequate referral of patients are positively linked to acceptance of oral cancer screening from a health-care provider and a health-care system perspective, respectively.

5.4.4 Effectiveness of screening

(a) Preventive effects of screening

One RCT (in India) and three observational studies – two based on the same screened cohort in Taiwan (China) and one in Cuba – have assessed the effect of screening individuals at high risk (defined in the studies as users of tobacco, alcohol, and/or betel quid) with clinical oral examination on incidence of advanced oral cancer and on mortality from oral cancer. In the RCT, after 15 years of follow-up, in users of tobacco and/or alcohol the relative risk of incidence of advanced oral cancer was 0.79 (95% CI, 0.65–0.95) and the relative risk of oral cancer mortality was 0.76 (95% CI, 0.60–0.97). The relative risks in the observational studies were very similar to those observed in the RCT, with reductions of 21–22% for incidence of advanced oral cancer and 24–26% for oral cancer mortality, and the findings were statistically significant in the cohort studies.

The studies were heterogeneous in the design of the screening intervention. The observational studies were based on evaluations of the performance of the national screening programmes, which included mainly male participants. Most

of the studies did not identify an impact of oral cancer screening on incidence of oral cancer overall.

(b) Harms of screening

Screening programmes may be associated with some harms, and it is important to consider the balance of benefits and harms for any screening activity. The potential harms of screening are associated with false-positive tests, false-negative tests, overdiagnosis, and overtreatment. Information about the harms of oral cancer screening is lacking.

5.4.5 Risk-based model for screening

Cancer screening has historically been based on age, without any assessment of exposure to known risk factors. Selectively screening only individuals at high risk may improve the efficiency and effectiveness of screening while minimizing the harms. A reanalysis of the findings of the RCT in India showed that a tailored approach based on alcohol consumption and use of any tobacco by the individuals increased the efficiency of oral cancer screening. A risk-based model for screening has been considered to be an appropriate approach for resource-limited countries with a high incidence of oral cancer.

6. EVALUATIONS, STATEMENTS, AND CONSIDERATIONS

6.1 Impact of quitting exposure to a risk factor on incidence of or mortality from oral cancer

6.1.1 Tobacco smoking

There is *sufficient evidence* that quitting tobacco smoking reduces the risk of oral cancer.

The risk decreases with increasing time since quitting smoking.

Rationale. *IARC Handbooks* Volume 11, published in 2007, already concluded that the risk of oral cancer decreases with increasing time since quitting smoking. Thus, in updating this evaluation, the Working Group restricted its review to recent studies that reported risk of oral cancer by time since quitting smoking, adjusted for important confounders. Recent evidence also reported a reduction in risk of oral cancer within 10 years of quitting smoking; the relative risk in former smokers reaches the relative risk in never-smokers after ≥ 20 years of cessation. The Working Group also reviewed the available evidence on smoking cessation and risk of leukoplakia, which suggests that the risk of leukoplakia decreases after quitting smoking.

Additional considerations. Quitting smoking has additional benefits; it reduces the risk of other chronic diseases, such as vascular diseases (coronary heart disease, cerebrovascular disease, aortic aneurysm, and peripheral arterial disease), non-malignant lung disease, other cancer types, and oral health problems.

Given that the joint effect of tobacco smoking and alcohol consumption is greater than multiplicative, quitting smoking reduces the large risk of oral cancer in individuals who continue to drink alcohol; this is an indisputable additional benefit of quitting smoking. Large reductions in risk would also be expected after smoking cessation in dual users of other agents known to be associated with oral cancer and correlated with tobacco smoking for which greater-than-additive or greater-than-multiplicative interactions have been established (i.e. smokeless tobacco, areca nut).

6.1.2 Alcohol consumption

There is *sufficient evidence* that cessation of alcohol consumption reduces the risk of oral cancer.

The risk decreases with increasing time since cessation of alcohol consumption.

Rationale. In reaching this evaluation, the Working Group gave more weight to studies that reported risk estimates by time since cessation of alcohol consumption; supporting evidence was provided by studies that reported risk estimates in former drinkers or current drinkers relative to never-drinkers. Studies that adjusted for

multiple potential confounders were also given more weight in the evaluation.

The evidence comes mainly from one large pooled analysis of data from 13 case–control studies, conducted in Asia, Europe, and North and South America. Although the original case–control studies have limitations in terms of recall bias and selection bias and there is significant heterogeneity in the pooled analysis, robust methodologies were used for data harmonization and statistical analyses, and consistent patterns of reduced risk after cessation of alcohol consumption were observed.

Additional considerations. The reduction in risk of oral cancer becomes more apparent after 10 years of cessation of alcohol consumption. There is some evidence that the reduction in risk of oral cancer is greater in former heavy drinkers (≥ 3 drinks per day).

Increased reductions in risk would also be expected after cessation of alcohol consumption in dual users of other agents known to be associated with oral cancer and correlated with alcohol consumption for which greater-than-additive or greater-than-multiplicative interactions have been established (i.e. smoked tobacco, smokeless tobacco, areca nut).

6.1.3 Smokeless tobacco use

There is *inadequate evidence* that quitting use of smokeless tobacco reduces the risk of oral cancer.

Rationale. In evaluating the body of evidence on risk of oral cancer upon quitting exposure to different risk factors, the Working Group gave the most weight to cohort studies and case–control studies that reported risk of oral cancer by time since cessation. In the case of smokeless tobacco, no studies were available based on this criterion.

The body of evidence supporting the evaluation consisted of two cohort studies and four case–control studies, conducted predominantly in Sweden and thus not providing data from other world regions where use of smokeless tobacco is highly prevalent.

The available studies had major limitations, including the absence of a clear period of abstinence in the definition of former users of smokeless tobacco, sparse numerical representation, and lack of sufficient adjustment for potential confounding factors.

Data from eight studies on the association between former use of smokeless tobacco and risk of oral potentially malignant disorders (OPMDs) were inconsistent.

Additional considerations. The Working Group noted the minimal geographical diversity in the studies, particularly the absence of studies from countries in South Asia, the world region that has the highest prevalence of use of smokeless tobacco. The Working Group also noted the absence of studies for smokeless tobacco products other than moist snuff, except for one small study on *shammah* use in Yemen.

6.1.4 Chewing areca nut products (including betel quid) with or without tobacco

There is *sufficient evidence* that cessation of use of areca nut products (including betel quid) with or without tobacco reduces the risk of oral cancer.

Cessation of use of areca nut products (including betel quid) with or without tobacco also reduces the risk of OPMDs.

Rationale. The Working Group elected to conduct a combined evaluation for chewing areca nut products without tobacco and chewing areca nut products with added tobacco, in view of several considerations. First, chewing behaviours and use of areca nut products are very heterogeneous between geographical regions and subregions. Second, the available literature does not enable a separate evaluation for each product.

The Working Group based the evaluation on data from published studies and from primary

analyses, using principally evidence on time since cessation, supported by the comparison of former users versus current users, and age at quitting. Particular attention was given to adjustment for important confounders and to the precision of the risk estimates. Three cohort studies had large sample sizes and long follow-up periods, which strengthened the temporal relationship between time since cessation and risk of oral cancer.

Key observations that guided the Working Group in making this evaluation include:

- Three large cohort studies and two case–control studies consistently showed a statistically significant association and statistically significant trend of reduced risk of oral cancer with increasing time since cessation of chewing areca nut products without tobacco.
- For cessation of chewing areca nut products with added tobacco, although the evidence was inconsistent across published studies, one large cohort study showed reduced risk of oral cancer with increasing time since cessation in former chewers.
- Risk reductions were also observed for OPMDs with increasing time since cessation of chewing areca nut products without tobacco, and for leukoplakia after cessation of chewing areca nut products with added tobacco.

Additional considerations. Cessation of chewing areca nut products with or without tobacco would be broadly beneficial for a reduced global burden of oral cancer. In addition to oral cancer and OPMDs, quitting chewing could prevent other cancer types (e.g. cancers of the pharynx and of the oesophagus) and other chronic diseases.

6.1.5 HPV16 infection

There are no studies to date on vaccination-related reductions in oral infection with human papillomavirus type 16 (HPV16) resulting in reduction in the incidence of HPV-associated oral cancer or oropharyngeal cancer. HPV vaccination has been shown to result in reduction in the prevalence of oral HPV16 infection in vaccinated individuals and in populations with high vaccination coverage. HPV vaccination has also been shown to result in reduction in the incidence, prevalence, and persistence of vaccine-type HPV infections, reduction in the incidence of associated precancers at the cervix, vagina, vulva, penis, and anus, and reduction in the incidence of cervical cancer in vaccinated individuals and in populations with high vaccination coverage.

There is a strong rationale and analogy, based on observations at other anatomical sites, that HPV vaccination would result in reduction in the incidence of HPV-associated oral cancer and oropharyngeal cancer in vaccinated individuals and in the populations at large, depending on vaccination coverage.

6.2 Interventions for cessation of smokeless tobacco or areca nut use

6.2.1 Behavioural interventions in adults

There is *sufficient evidence* that behavioural interventions in adults are effective in inducing quitting use of smokeless tobacco.

Rationale. Nine studies (seven randomized controlled trials and two cohort studies), including several high-quality studies, were available for evaluation. A positive effect of the intervention on the quit rates was observed consistently in the body of evidence, and chance, bias, and confounding as causes of this association were ruled out with reasonable confidence. Despite some limitations, all the studies showed a positive association, and six of the studies showed statistically significant effects.

6.2.2 Behavioural interventions in youth

There is *limited evidence* that behavioural interventions in young people are effective in inducing quitting use of smokeless tobacco.

Rationale. Five studies (four randomized controlled trials and one cohort study) were available for evaluation. The body of evidence provided apparently inconsistent results: one study showed significant effects, three studies showed non-significant positive effects, and one study showed a non-significant negative effect. However, this could be explained as follows:

- In the study that showed significant effects on the quit rates, the control arm had no intervention.
- Three of the four studies that showed non-significant effects, two positive and one negative, had some form of intervention in the control arm, thus pulling the estimates towards the null.

In addition, one study reported a significant positive effect of the intervention on the prevention of initiation of smokeless tobacco use.

6.2.3 Pharmacological interventions

There is *limited evidence* that pharmacological interventions with nicotine replacement therapy or antidepressants (escitalopram and moclobemide) are effective in inducing quitting use of smokeless tobacco and areca nut with tobacco.

Rationale. Three randomized controlled trials were available for evaluation. Two studies assessed the effectiveness of nicotine replacement therapy (one with gum and one with lozenges), and one study assessed the effectiveness of antidepressants (escitalopram and moclobemide). All three studies followed a good methodology, had adequate controls, and used proper outcome measurements. However, the studies had several limitations, including short follow-up periods (< 12 months) and confounding by the presence of some dual users (tobacco smoking and smokeless tobacco use).

Two studies showed an effect of the intervention in inducing quitting; one was statistically significant, and one was non-significant. The third study showed no effect. However, in the latter two studies, the control groups were provided with behavioural intervention instead of placebo, thus reducing the potential effect size.

6.2.4 Combined pharmacological and behavioural interventions

There is *limited evidence* that combined pharmacological and behavioural interventions are effective in inducing quitting use of smokeless tobacco.

Rationale. A large number of randomized controlled trials (16) were available for evaluation. A positive effect of the intervention on the quit rates was observed in some studies, but chance, bias, or confounding could not be ruled out with reasonable confidence, for several reasons:

- A positive effect of the intervention was reported in most studies (13 of 16). However, in most of these studies (11 of 13), the association was not statistically significant.
- Eight of the studies had large study populations (≥ 100 participants in each arm) and long follow-up periods. However, only two of these eight studies showed significant effects.
- Most studies had the same behavioural intervention in the control arm, thus pulling the estimates towards the null.

6.2.5 Policies

Few data are available on the effect of the individual World Health Organization Framework Convention on Tobacco Control policies on smokeless tobacco control. The strongest effect, despite limited evidence, was shown for taxation in reducing the prevalence of smokeless tobacco use. One study in India showed a positive effect of school-based tobacco control policies. A combination of policies was shown to be more effective than a single policy.

There is a shortage of data with regard to the effect of control policies for areca nut products, because these policies are new and have been implemented recently. The limited but positive results from Taiwan (China) suggest that adoption of a comprehensive set of policies to control areca nut use may lead to reductions in the prevalence of areca nut use.

6.3 Screening for oral cancer and OPMDs

6.3.1 Effectiveness of screening by clinical oral examination

Screening of individuals at high risk by clinical oral examination *may reduce mortality from cancer of the oral cavity* (Group B).

Individuals at high risk are defined as those with tobacco use, areca nut use, alcohol consumption, or a combination of these, in any form.

Rationale. In reaching this evaluation, the Working Group noted the following:

- The randomized controlled trials and cohort studies showed a statistically significant positive effect of oral screening on the incidence of advanced oral cancer and on oral cancer mortality in individuals at high risk (based on tobacco use, areca nut use, alcohol consumption, or a combination of these, in any form).
- The impact of oral screening on oral cancer mortality in the general population cannot be established on the basis of the current evidence.
- The limited number of studies of different designs (one randomized controlled trial, two cohort studies, and one case–control study) in a few settings restricts generalization of the outcomes.
- The limitations of the included studies were likely to pull the effect of screening towards the null:
  - In the randomized controlled trial, there was low compliance of screen-positive cases with further assessment.
  - In the cohort studies, there was selection bias for screening, and possible contamination of the control group.
  - In the case–control study, there was lack of power, possible overestimation of exposure to the intervention (defined as "any visit to a community dentist"), and a low coverage of the programme.
- The included studies did not report whether there were any primary prevention interventions within the studied population, which could have an impact on the estimates.
- The included studies had other limitations with an unclear effect on outcome:
  - The randomized controlled trial used a small number of randomized units.
  - In the retrospective cohort study, the proportion of individuals at high risk in the control group was unclear, possibly leading to information bias.

Regimen to which the evaluation applies. The screening interval used in the included studies was either 2 years or 3 years. The optimal age range could not be established.

6.3.2 Additional considerations

(a) Adjunctive techniques to oral examination

Very few studies have evaluated adjunctive techniques in population screening studies. Most of the adjunctive techniques have been evaluated as diagnostic adjuncts in either prospective accuracy studies or retrospective cohort or case–control studies. All of the available studies report accuracy measures of test results against histopathology as the reference standard. Given the unknown natural history of OPMDs in an individual patient, it is challenging to extrapolate accuracy data to important end-points such as mortality or survival. The added value of adjunctive techniques to clinical oral examination remains unknown. There is a potential for using adjunctive techniques and biomarkers in saliva for the diagnosis of OPMDs and oral cancer. However, there is a lack of clinical validation linked to important end-points as a standalone method in oral cancer screening settings.

(b) Harms of screening

A clear understanding of the harms linked to false-positive screening test results and, more importantly, false-positive diagnostic findings leading to potential overtreatment is hampered by a poor understanding of the natural history of OPMDs. There is currently little evidence that adjunctive techniques can reduce the proportion of false-positive results when screening by clinical oral examination. Adjunctive techniques or biomarkers that are predictive for cancer progression in OPMDs are being investigated. Quality assurance of programme implementation is important to improve the performance of screening programmes and reduce the harms of screening. This issue has not been addressed in the primary studies reviewed by the Working Group.

(c) Risk-based model for screening

Assessment of risk, for example by questionnaire, has the potential to increase programme efficiency and reduce the harms of overscreening, overdiagnosis, and overtreatment. However, implementation of screening programmes using risk-based models for selection of participants is a challenge from a programmatic perspective.

(d) Monitoring and evaluation of screening programmes

Assessment of determinants of partici-pation at all steps of the screening pathway has been demonstrated to be critical for the optimization of cancer screening at other sites (e.g. cervix, breast, and colon). The existing oral cancer screening programmes lack proper monitoring and evaluation mechanisms, preventing evidence-based evaluation of their efficacy and health impact.

It remains unclear whether the known risk factors for oral cancer, as well as age and sex, are positive or negative determinants of participation in oral cancer screening. Identifying and describing the predictors of participation in oral cancer screening, provider training, compliance with referral, the quality of available data, and the interventions to improve these is critical to increase the effectiveness of oral cancer screening programmes. Filling this gap may enable policy-makers and stakeholders to efficiently allocate human and financial resources to obtain higher benefits and reduce inequalities.

The screening trials have not provided a clear understanding of the natural history of OPMDs. The impact of detection, treatment, and surveillance of patients with OPMDs on oral cancer incidence and mortality has not been determined. Among the studies that assessed cancer incidence, most did not observe an impact of oral cancer screening on oral cancer incidence.

The Working Group considers primary prevention to be an integral part of a screening programme.

IARC HANDBOOKS

A Working Group of 25 independent international experts, convened by the International Agency for Research on Cancer (IARC) between September and December 2021, reviewed the scientific evidence on primary and secondary prevention of oral cancer. Cancer of the lip and oral cavity ranks 16th in cancer incidence and mortality worldwide and is a common cause of cancer death in men across much of South and South-East Asia and the Western Pacific. The main causes of oral cancer worldwide are tobacco smoking and alcohol consumption. Smokeless tobacco use and areca nut use are the leading causes in those countries where their use is prevalent.

This is the first evaluation of oral cancer prevention by the *IARC Handbooks* programme. The Working Group reviewed the body of evidence and provided evidence-based evaluations of the impact of cessation of exposure to risk factors, of cessation interventions for products containing smokeless tobacco or areca nut, and of screening for oral cancer by clinical oral examination. In addition, this publication presents background information related to oral cancer, such as the global burden of oral cancer, the prevalence of use of products containing smokeless tobacco or areca nut, and emerging technologies for oral cancer screening.

This volume of the *IARC Handbooks* brings together, for the first time, all the available evidence related to primary and secondary prevention of oral cancer.