Detectable by screening

Appearance of

Diagnosis

Start o...

"Usual care"

Diagnosis

Start of
treatment

Earlier diagnosis by

better awareness

Diagnosis

Start of
treatment

Screening

Earlier treatment

Time

CANCER SCREENING AND EARLY DIAGNOSIS

CANCER SCREENING AND EARLY DIAGNOSIS

Given the vastness of the field of cancer research and the imperative of being at the cutting edge, IARC's activity was from the outset focused predominantly on cancer research for cancer prevention, and – within that domain – on epidemiological and laboratory-based research on cancer-causing agents as a route to primary prevention. In addition, some topics of investigation were developed in the area of early diagnosis of cancer precursor lesions, i.e. secondary prevention, in particular for cancer of the uterine cervix. The importance of early – or, at the very least, timely – diagnosis of cancers common in developing countries with scarce medical facilities quickly became clear. Thus, more IARC research was channelled into these countries. Projects on early detection combined the advancement of scientific knowledge with the development and strengthening of local infrastructures for diagnosis and treatment.

> " *I was with the first delegation of IARC going to a very remote area of rural China for two to three months, and we were the first foreigners to go there. We probably did what were the first intervention studies trying to prevent precancerous lesions with vitamins.* – Nubia Muñoz, former IARC scientist

In the early 1980s, IARC conducted a pilot project: a moderately sized preventive trial in a population with a high frequency of oesophageal cancer, in Henan Province in China. No effect could be demonstrated of vitamin and zinc dietary supplements on detectable precursor lesions of oesophageal cancer. In the mid-1990s, IARC also investigated the effects of vitamin A and β-carotene dietary supplements on oral leukoplakia, a precursor lesion for oral cancer, in a small-scale trial among fishermen and women in India. Evidence of remission of lesions indicated the value of conducting longer-term trials with vitamin A supplementation. In parallel with these activities and early work on cancer screening, IARC initiated the Handbooks of Cancer Prevention, as well as other evaluative reviews, which included several screening programmes.
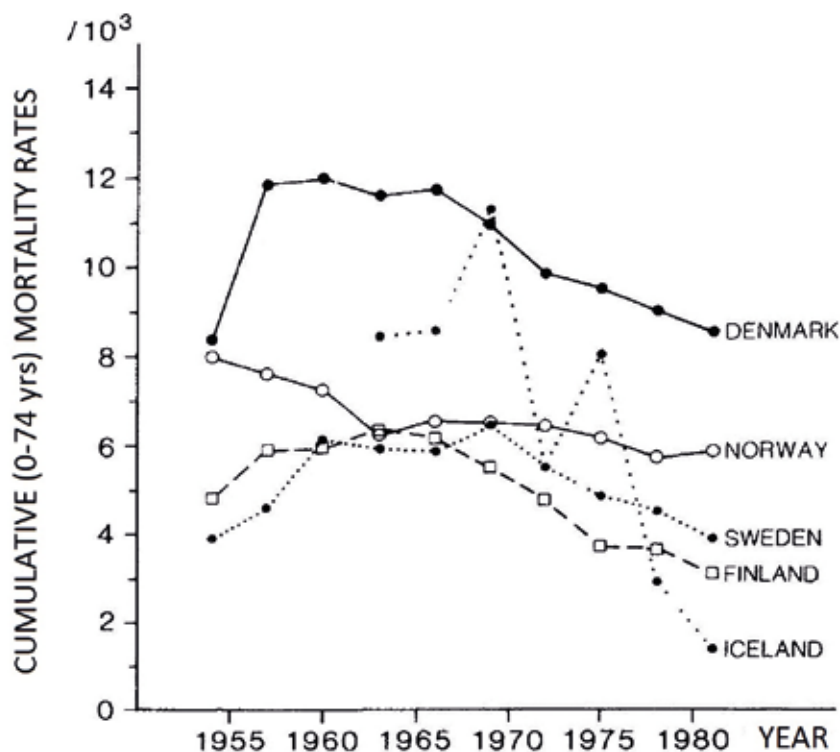
CERVICAL CANCER SCREENING

In developed countries

In the past 50 years, cervical cancer incidence and mortality have dropped markedly in most developed countries, which is where the first clear evidence of the effectiveness of screening for cancer emerged.

Trends in the cumulative mortality rates (ages, 0–74 years) from cervical cancer in the Nordic countries. Between 1965 and 1982, the mortality decreased in all five countries. Apart from the introduction of the screening programmes, there had been no other major changes in the health care systems since the mid-1960s that would appreciably affect mortality from cervical cancer. After 1965, mortality fell by 84% in Iceland, by 50% in Finland, and by 34% in Sweden; these three countries had organized nationwide screening programmes. Mortality fell by 27% in Denmark, where the screening programme was introduced in some counties, and by 11% in Norway, where there was an organized programme in only one county.

A clinical diagnosis of cancer is confirmed once the microscopic examination of tissue specimens has shown the histological features characteristic of a malignancy. The microscopic examination of exfoliated cells from the tissue also provides information, and George Papanicolaou first suggested, in 1928, that this could prove valuable for early diagnosis of cervical cancer. By the 1940s, the feasibility and simplicity of the cytological examination of the cervix, or "Pap smear", had been established in the USA. As Michael Shimkin noted, "Since the procedure does recognize an important cancer before it is invasive, its full application would significantly reduce mortality from cervical cancer." The logic of this argument seems unassailable, and – moving beyond cervical cancer to other malignancies as well as other diseases – it has become the rationale for all attempts to recognize and treat a disease in its early stages (see "Screening for cancer: theory and reality").

The effectiveness of Pap smear screening was supported by a collaborative analysis by scientists at IARC and in Finland of the trends in mortality from cervical cancer in the Nordic countries. By 1980, more than three quarters of women had undergone screening in all five countries (Denmark, Finland, Iceland, Norway, and Sweden). Between 1953 and 1982, cervical cancer mortality stopped rising and started to fall in all five countries, accompanied since the mid-1960s by a decrease in the occurrence of new clinical cases.

SCREENING FOR CANCER: THEORY AND REALITY

The figure depicts the clinical history of a person developing a cancer that is diagnosed under three different circumstances, corresponding to different time points in the natural course of the disease. In circumstance A, the diagnosis is made because of the appearance of symptoms, i.e. when the disease is in its clinical phase. There is usually a delay between the appearance of symptoms and the start of treatment of a cancer. The person's life expectancy after the treatment may, even today, be fraught with unpleasant consequences because of possible complications of the disease and side-effects of treatment. In situation B, earlier diagnosis (during the clinical phase) and treatment are possible due to better awareness of symptoms by the patient, the patient's close relatives, and the physician. This may lead to some increase in life expectancy and some reduction in serious consequences of the disease. In circumstance C, the cancer is recognized before symptoms appear, i.e. in the preclinical phase, when it is detectable by screening tests (which always need to be confirmed by a full diagnostic work-up). The earlier detection and treatment may result in an appreciably longer life expectancy, with less serious consequences of treatments because they may be applicable in less drastic forms to the initial stage of the disease.
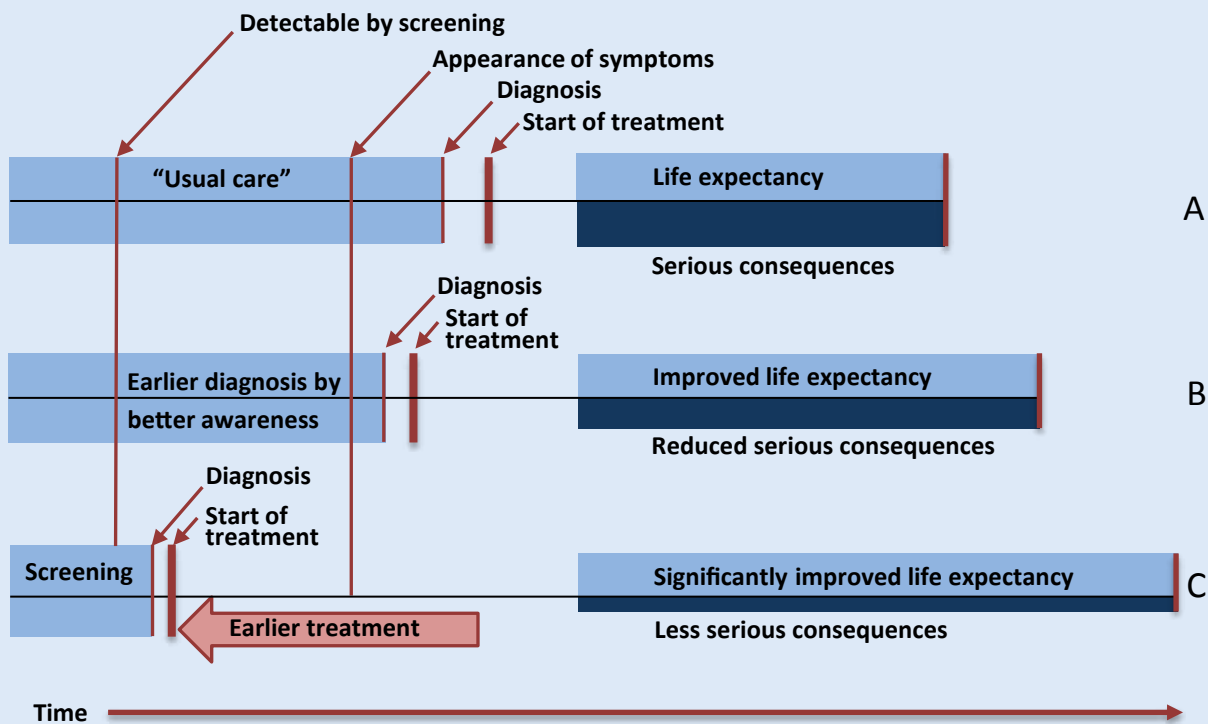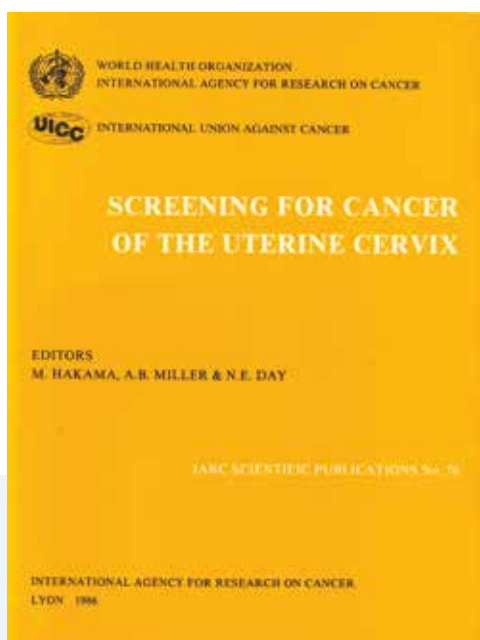

Early detection of cancers through symptoms or by screening.

In theory, situation C makes sense biologically and clinically, but does it actually occur when a screening programme is systematically offered to a population? What if the sole result of earlier detection and treatment is that a person lives a longer time as a recognized cancer patient but not a longer life? These questions can be rigorously addressed only by epidemiological studies in which subjects are assigned at random either to undergo scheduled periodic screening for, say, cervical cancer or to simply be followed up according to standard local

medical practice. A cervical cancer screening programme would be demonstrated to be effective if mortality from cervical cancer were lower in the screened group than in the unscreened group. An evaluation trial of this kind, involving thousands of people over several decades, poses complex organizational challenges and requires considerable resources. However, such trials have been conducted on various screening programmes for cancers of the breast, ovary, colon and rectum, lung, and prostate. No such trial has ever been carried out for screening of cervical cancer because the widespread acceptance of the Pap smear among doctors and women alike made it ethically unacceptable to conduct a study in which the test would deliberately not be offered to a group of women.

IARC Scientific Publication No. 76, *Screening for Cancer of the Uterine Cervix*, was published in 1986 as a joint initiative of IARC and UICC. The papers collected in this publication provide detailed information on the screening programmes in the Nordic countries and other countries, and review the evidence on the effectiveness of the programmes. Optimal ages and frequency for screening are also discussed. By the mid-1980s, a clear consensus prevailed, based on epidemiological studies of the observational type but without any evidence from randomized trials, that programmes of systematic screening using the Pap smear test are effective in reducing occurrence of cervical cancer and mortality from the disease.

> "
> *IARC was involved in really important publications that became landmark papers on the evaluation of cervical cancer screening, proving very important for the next 20 years.*
> – Max Parkin, former IARC scientist

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

UICC INTERNATIONAL UNION AGAINST CANCER

SCREENING FOR CANCER OF THE UTERINE CERVIX

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IARC SCIENTIFIC PUBLICATIONS No. 76

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
LYON 1986

In developing countries

Over several decades, population-based cervical cytology screening programmes offering the Pap smear test to women every two to four years have reduced cervical cancer incidence and mortality by up to 80% in the developed countries of Australia, Japan, and New Zealand, as well as those in Europe and North America. However, of the more than half a million new cases of cervical cancer each year worldwide, 85% occur in developing countries. It is in these areas that a majority are diagnosed at an advanced stage, and in parts of Africa, Asia, and Latin America, 5-year survival rates for cervical cancer frequently fall below 50%.

In low-income countries, screening programmes are often non-existent, and in middle-income countries they have often performed poorly. Introducing and maintaining a high-quality Pap smear service for a large population is challenging. Moreover, women with an abnormal test result should usually receive a confirmatory diagnosis through microscopic examination of a biopsy specimen by a histopathology specialist – a service that is often unavailable in low-resource settings. The recognition of these limitations for cervical cancer screening in low- and middle-income countries has led to the development of alternative, simpler screening methods.

Women at a health centre in India waiting to receive cervical cancer screening.

IARC has provided impetus to these endeavours through an approach that has combined research on the performance of alternative methods with the establishment and consolidation of the health services needed for large-scale application (see "Research projects linked to health services development"). A major IARC collaborative investigation involved more than 130 000 women aged 30–59 years living in 497 villages in one district in the western state of Maharashtra in India. The villages were randomly allocated to four different intervention procedures; all the women in a village received the same procedure. The women were followed up for at least 8 years to record occurrence of cervical cancer and mortality from the disease.

When the four procedures were compared after 8 years, the best outcome was seen for screening by testing for the presence of human papillomavirus (HPV) DNA (see the chapter "From laboratory to population"). The next best outcome was for the simplest of the four procedures: visual inspection of the cervix with acetic acid. In this technique, the cervix is examined by colposcopy (inspection of the vagina and cervix using magnifying lenses) after acetic acid is applied with a cotton swab. If an abnormal aspect of the cervical surface is found, a full colposcopy examination is carried out to identify precancerous lesions. These can be treated immediately by cryotherapy (freezing cervical tissue with nitrous oxide), as in the study in India, or alternatives such as cold coagulation or a loop electrosurgical excision procedure.
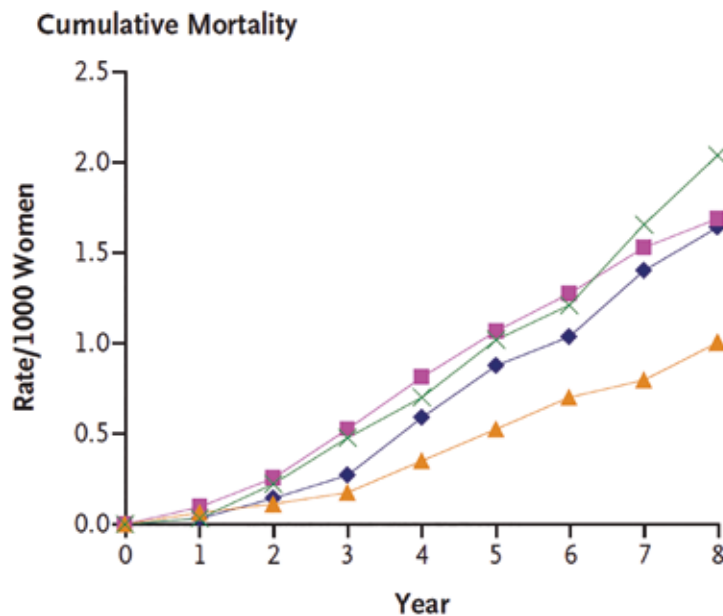
Cumulative mortality rates from cervical cancer over 8 years of follow-up in a screening study in rural India. The lowest mortality was seen in women screened by testing for human papillomavirus (HPV) DNA (yellow triangles). The next best intervention was visual inspection of the cervix with acetic acid (blue diamonds). Less favourable was the mortality of women screened by cytology (violet squares) and of the control group, who did not receive any specially programmed screening (green crosses).

RESEARCH PROJECTS LINKED TO HEALTH SERVICES DEVELOPMENT

Most IARC research projects on the evaluation of cancer screening in developing countries are also designed to be instruments for local development of regular health services, in a similar way to the vaccination project against hepatitis B virus in The Gambia (see the chapter "Viruses and vaccines"). Rengaswamy Sankaranarayanan comments on this hallmark of IARC field research.

"We wanted the research to be a vehicle, not only to address a research question but also for our project afterwards to develop into a service programme for early detection. It creates a lot of interest for the local people to continue the early detection activity, drawing in more people and acting as a catalyst to develop wider early detection programmes in the region and in the country. Being a clinician, I was well aware of the relevance of early detection for successful treatment. Hence, wherever we mounted a research project we looked at it in a comprehensive way, addressing the research question as well as the practicalities of how to train people in diagnosis and treatment in order to improve the local cancer control facilities.

"For these purposes, we made optimal use of the position of IARC as a research organization within the framework of the World Health Organization (WHO), with its links to national governments and health services authorities. We had the double advantage of being perceived and treated as belonging to a research institution with recognized high academic standards that at the same time has a public health role as a WHO agency.

"IARC has become much more visible in several developing countries because of the approach of combining research with health services development. Detecting cancer when it is still asymptomatic or soon after people have symptoms gives immediate visibility to those carrying out the detection and treatment programme. In the case of cervical cancer, we have been the main exponents of the single-visit approach, where screening, diagnosis, and treatment are all done on the same day. Maybe this will lead to more low- and middle-income countries calling on IARC to contribute on the basis of its successful experiences in the development of uniform control policies for cancers."

Such "see-and-treat" interventions, where screening, diagnosis, and treatment are all performed in a single session, can be especially valuable to ensure compliance in rural settings, where women may have to travel long distances to reach modestly equipped health centres. In view of its feasibility and affordability, the "screen-and-treat" approach based on visual inspection of the cervix with acetic acid has been tested for wide implementation in numerous countries, including some in Asia (Bangladesh and Thailand) and in Africa (Angola, Burkina Faso, the Congo, Guinea, Mali, the Niger, and the United Republic of Tanzania). Notably, IARC has been instrumental in providing
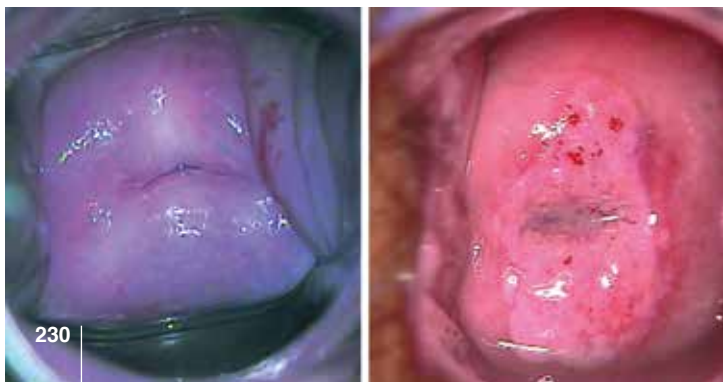
Outcomes of visual inspection of the cervix with acetic acid. There is a marked difference in appearance between a normal cervix (left) and one with a lesion suggestive of cervical intraepithelial neoplasia, an early stage of cervical cancer.

training to health care professionals in this approach, and thus has been able to translate the research through to adoption in such settings.

ORAL CANCER SCREENING

About 300 000 new cases and 150 000 deaths from oral cancer occur each year worldwide. Two thirds of these occur in developing countries, and one third in the Indian subcontinent, where oral cancer is the most common malignancy in men. This high risk is related to the high frequency of chewing mixtures containing agents that have been classified as carcinogenic by the IARC Monographs Programme. If the cancer is not detected and treated at an early stage, the 5-year survival rates are low (40% or less). Oral cancer is thus an obvious candidate for screening, given that the oral cavity is easily accessible for inspection.

In the Indian subcontinent, many people enjoy chewing paan, a mixture containing betel leaf combined with lime, areca nuts, and sun-cured tobacco.

A large IARC-coordinated randomized trial testing the visual screening of oral cancer was conducted in the state of Kerala, at the south-western tip of the Indian subcontinent. The trial involved almost 200 000 men aged 35 or older belonging to 13 local populations. Seven of the populations were assigned to three rounds of visual screening over an 8-year period. The other six populations represented the control arm of the trial, assigned to the standard health care prevailing in Kerala. The visual examination was performed by university graduates in non-medical subjects who had been trained to recognize lesions that could be precancerous or cancerous. Screening followed by referral for treatment was shown to reduce mortality from oral cancer, particularly among men at high risk because of tobacco use and/or alcohol consumption; for this group there was a 30% reduction in oral cancer mortality rate compared with the control group. For these men at high risk, when all the costs incurred by the screening programme were added up, the cost increase over the standard care as provided in Kerala amounted to about US$ 150 per year of life saved, which is not an unreasonable cost even in a moderate-resource setting.

COLORECTAL CANCER SCREENING

Cancer of the colon and rectum is the third most common cancer globally, and its incidence is increasing in many developing countries. In fact, incidence of colorectal cancer increases in conjunction with improvements in the level of human development worldwide. Early detection and removal of adenomatous

Visual examination of the colon mucosa enables not only the recognition but also the removal of cancer precursor lesions like polyps. The magnified image at lower right shows a bowel polyp being clasped for excision. Assessing the needs and building the capacity for clinical diagnosis and treatment is a crucial part of the implementation of a successful programme.

(glandular) polyps has been shown to be effective in developed countries. There is a need to implement programmes of screening plus treatment in developing countries, preferably in advance of the projected increases in incidence of the disease.

IARC has started to support the establishment of such programmes, and very recently results have become available of a large pilot implementation project in Thailand. The study, conducted by researchers from IARC and the National Cancer Institute in Thailand, involved a target population of nearly 130 000 adults aged 50–65 years in Lampang Province. The faecal blood occult test was used as the screening instrument, followed by colonoscopy in people with occult blood in the faeces. Polyps seen at colonoscopy were removed during the examination, and suspected cancerous lesions were referred for further investigation and treatment according to standard protocols.

The study was carried out in real-world conditions using the existing routine health care facilities in Lampang Province. The preliminary results documented the feasibility, acceptance, and safety of the procedures of an organized screening programme to which people are invited and in which a high proportion participate. Observations included higher participation rates in rural areas than in urban areas and among women than among men. These findings were used in the subsequent scaling up of the programme to other provinces. It is notable that the integration of a research study within a national programme in this way is efficient, adding value for modest additional cost.

> "
> *A major challenge to implement change, when you have found the resources, is that you need the health service capacity, a health service infrastructure to deliver what you want to deliver in an efficient manner.*
> – Rengaswamy Sankaranarayanan, IARC scientist

THE IARC HANDBOOKS OF CANCER PREVENTION

The first volume of the IARC Handbooks of Cancer Prevention was published in 1997 and dealt with non-steroidal anti-inflammatory drugs (NSAIDs), consistent with a view at the time that chemoprevention could provide a valuable approach for cancer control. The express purpose of the Handbooks, as a complement to the IARC Monographs, was to evaluate scientific information on agents and interventions that may reduce the incidence of or mortality from cancer. The Handbooks were developed with their own Preamble, which defined the procedures for evaluating chemopreventive agents, a scope later enlarged to cover evaluation of other types of preventive interventions, including primary prevention and cancer screening.
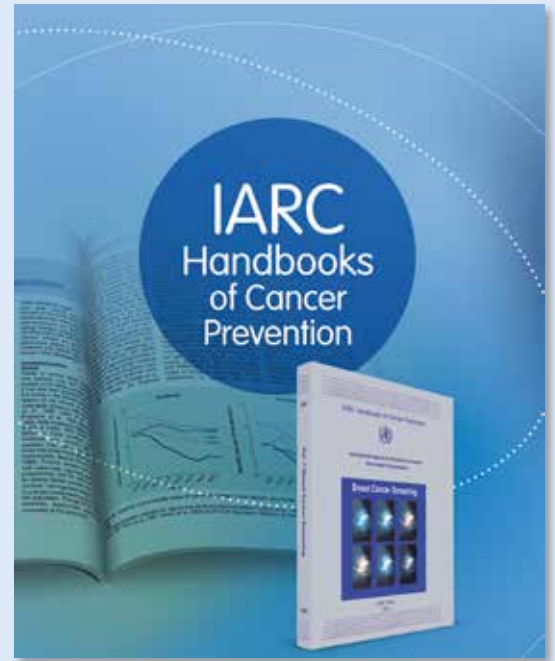
To date, the Handbooks have covered topics such as preventive agents (e.g. NSAIDs, vitamin A, carotenoids, and retinoids), preventive actions (e.g. use of sunscreens, weight control and physical activity), screening (cancers of the breast and cervix), and various tobacco control measures. The Handbooks were relaunched in 2014, and the first in the new series was a reassessment of breast cancer screening. Volumes on screening for cancers of the cervix (update) and cancers of the prostate, lung, and colorectum (first-time evaluations) are foreseen.

The overall intention of the Handbooks is to assist national and international authorities in devising programmes of health promotion and cancer prevention and in assessing the benefits and risks of a particular intervention. There is a major demand worldwide for such evaluations in order to improve public health; IARC is ideally placed to respond based on its expertise, experience, reputation, and independence.

REVIEWING THE EVIDENCE ON SCREENING PROGRAMMES

The IARC Handbooks of Cancer Prevention series evaluates the evidence for preventive interventions (see the chapter "Carcinogens in the human environment"). Volume 7 of the series, published in 2002, evaluated breast cancer screening. The Working Group responsible for that volume concluded that there was sufficient evidence from randomized trials for the efficacy of screening women aged 50–69 years by mammography as the sole screening modality in reducing their mortality from breast cancer. However, the Working Group formulated several qualifications, in particular concerning the substantial uncertainty about the best frequency of screening and the adverse effects, given the fact that 50–90% of women found positive at the mammographic test would turn out not to have breast cancer upon completion of the confirmatory diagnostic procedures. Subsequently, debates about these open issues became more heated after the statistical reanalyses of data from the available studies.

CLINICAL BREAST EXAMINATION: IS IT EFFECTIVE?

Organized mammography screening is often neither affordable nor feasible in low- and middle-income countries, where breast cancer incidence and mortality are now rising. In such countries, a more feasible proposition is clinical breast examination (visual inspection and palpation by a skilled health worker). IARC has addressed the issue of evaluating its effectiveness through a collaborative study in the state of Kerala in India.

Clinical breast examination by trained health workers may offer a viable alternative to mammography-based screening.

More than 110 000 women aged 30–69 years with intact breasts and no history of breast cancer participated in the study. Depending on their electoral ward of residence (each ward formed a cluster of women), they were randomly assigned to the screening intervention or to standard health care. The clinical breast examination was performed by female health workers with a bachelor's degree who had undergone a 3-week structured training course. The health workers provided the examination, which took on average 6–9 minutes, to women in their homes, at a nearby health centre, or in a makeshift clinic in the area. Women found positive at the clinical breast examination because of suspicious findings were referred to a breast clinic set up at the screening project office for further investigation; if breast cancer was confirmed, they underwent treatment.

Three rounds of screening some years apart were planned. After the first round, the screened group showed a higher frequency of early-stage breast cancer than the control group and a slightly lower frequency of advanced breast cancer. Although these results are consistent with a favourable effect of screening, a firm evaluation – particularly in terms of mortality – will become available only after the completion of the three rounds of screening.

In 2014, the IARC Handbooks of Cancer Prevention programme resumed when a Working Group was convened to re-evaluate the evidence on breast cancer screening (see "The IARC Handbooks of Cancer Prevention"). The Working Group's key conclusion – using the codified IARC criteria and language – was that there is sufficient evidence of a reduction of breast cancer mortality by mammography screening in women aged 50–74 years and that there is sufficient evidence that screening induces overdiagnosis of cancers (i.e. cancers detected by screening that would not otherwise have been diagnosed during a woman's lifetime). An obvious implication is that the balance of benefits and harms needs to be assessed carefully for each population, as characterized in particular by the frequency of breast cancer and the health resources available. The Working Group concluded that there is sufficient evidence that mammography

screening for women aged 50–69 years can be cost-effective in countries with a high frequency of breast cancer. Results on mortality reduction by modalities other than mammography-based screening were considered to be inconclusive (see "Clinical breast examination: is it effective?").

Over the years, IARC has provided its expertise in the preparation of World Health Organization guidelines for the screening and treatment of precancerous lesions to prevent cervical cancer and breast cancer. In addition, the findings from IARC research studies have contributed to the evidence base for the development of those guidelines, notably for cervical cancer. IARC has also made a major contribution by coordinating the European Cancer Network for Screening and Prevention in providing European guidelines for quality assurance in cervical, breast, and colorectal cancer screening. These guidelines have been highly influential in the development of national screening programmes across the European countries. Furthermore, in 2014 IARC coordinated the development of the fourth edition of the European Code Against Cancer, which consists of 12 recommendations. These "12 ways to reduce your cancer risk" focus on actions that people can take to lower their risk of cancer, including undergoing screening tests for cervical, breast, and colorectal cancers.

The website of the IARC Screening Group (screening.iarc.fr) offers a comprehensive overview of IARC's activities in the area of early detection and treatment of cancer, including training materials, scientific papers, field operating manuals, and guidelines for interventions.