

COLORECTAL CANCER SCREENING

VOLUME 17

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IARC HANDBOOKS OF
CANCER PREVENTION

WORKING PROCEDURES

The Working Procedures of the *IARC Handbooks of Cancer Prevention* describe the objective and scope of the programme, the scientific principles and procedures used in developing a *Handbook*, the types of evidence considered, and the scientific criteria that guide the evaluations. These Working Procedures apply to the evaluation of screening procedures and interventions.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 14.1 million in 2012 and is expected to reach 22.2 million by 2030 ([Ferlay et al., 2015](#)). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries.

Prevention of cancer is one of the key objectives of the International Agency for Research on Cancer (IARC). Cancer prevention can be achieved by primary prevention – aimed at preventing the occurrence of cancer – or by secondary prevention – aimed at diagnosing cancer sufficiently early to reduce related mortality and suffering.

Screening and early clinical diagnosis are the principal instruments of secondary prevention of cancer and a fundamental component of any cancer control strategy. Screening may enable detection of cancer sufficiently early that cure

and resulting reduction in mortality and having the disease are realistic possibilities given suitable treatment. Screening for some cancers, such as cervical or colorectal cancer, may also detect precancerous lesions, effective treatment of which can prevent occurrence of cancer.

When screening is planned as part of a cancer control programme, only procedures proved to be effective (see below) should be proposed to the general population. Screening usually requires repeated interactions between “healthy” individuals and health-care providers, which can be inconvenient and costly. Furthermore, effective screening requires an ongoing commitment between the public and health-care providers and has inherent public health costs.

2. Scope

[Cochrane \(1972\)](#) first discussed the concepts of efficacy and effectiveness in the context of health interventions. “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; the benefit or utility to the individual or

the population of the service, treatment regimen, or intervention. Ideally, the determination of efficacy is based on the results of a randomized controlled trial”. In contrast, the related term “effectiveness” was defined by the same author 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; a measure of the extent to which a health care intervention fulfils its objectives in practice”.

The distinction between efficacy as measured in experimental studies and the effectiveness of an intervention at the population level is a crucial one for public health decision-making. Efficacy is a necessary but not sufficient basis for recommending screening. The efficacy of a screening procedure can be inferred if effectiveness can be proven. Screening by a given procedure has sometimes been implemented on the assumption that “earlier is better,” even when no evidence of efficacy was available. If such interventions result in a significant reduction in mortality that cannot otherwise be explained, it can be inferred that the procedure is effective. However, uncontrolled interventions in which individuals are exposed to unknown risks and benefits should be avoided.

In addition, the fact that the effectiveness of a screening procedure may be different in different populations is often overlooked. Even when a screening procedure is effective at the population level, other outcomes, such as harm and costs and the potential for other interventions to achieve equivalent benefits, must be considered. A screening programme must satisfy certain minimal requirements (e.g. acceptability, availability of relevant personnel, facilities for screening, and access to pertinent health services) if it is to achieve the results that have been documented in experimental settings.

3. Objectives

The objectives of the Working Group are:

1. To evaluate the strength of the evidence for the preventive efficacy of a screening procedure;
2. To evaluate the strength of the evidence for the effectiveness of screening interventions in defined populations, taking into account the balance of benefit and harm in target populations;
3. To assess other outcomes related to the procedures, as appropriate.

The conclusions of the Working Group are published as a volume of the *IARC Handbooks of Cancer Prevention*.

4. Meeting participants

Five categories of participants can be present at a *Handbook* meeting:

1. The *Working Group* is responsible for conducting the critical reviews and evaluations. The tasks of Working Group Members are described in detail below. Working Group Members are selected on the basis of: (i) knowledge and experience; and (ii) absence of real or apparent conflicts of interests. They have often published significant research related to the screening strategies being reviewed, and IARC uses literature searches or consults with other experts in-house or externally to identify such experts. Consideration is also given to demographic and gender diversity and balance of scientific findings and views.
2. *Invited Specialists* are experts who also have important knowledge and experience, but have a real or apparent conflict of interests. They are invited when necessary to assist the Working Group by contributing technical knowledge and experience during subgroup and plenary discussions. They may contribute text on issues that do not influence the final

evaluation (see Part B, Sections 1 and 2), or review text prepared by the Working Group. Invited Specialists do not serve as meeting chair or subgroup chair, and do not participate in the evaluations.

3. *Representatives* of national and international health agencies may attend meetings when their agencies are sponsors of the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, do not draft any part of a *Handbook*, and do not participate in the evaluations.
4. *Observers* with relevant scientific credentials may be admitted to a meeting in limited numbers upon previous request. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. At the meeting, the overall chair and subgroup chairs may grant Observers an opportunity to raise questions or comments, generally after a Working Group discussion is concluded. Observers agree to respect the Guidelines for Observers at Meetings of the *IARC Handbooks of Cancer Prevention* (available at <http://handbooks.iarc.fr>).
5. The *IARC Secretariat* consists of IARC scientists who have relevant expertise. They participate in all discussions, and may serve as rapporteurs. When requested by the meeting chair or subgroup chair, they may also help draft text, prepare tables, or conduct analyses. They do not participate in the evaluations.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the “Declaration of Interests for IARC/WHO Experts” form to identify financial interests, employment and consulting activities, as well as individual or institutional research support related to the subject of the meeting. IARC assesses these declared interests

to determine whether there is a real or apparent conflict in relation to the topic under evaluation that warrants exclusion or some limitation on participation role. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants, as well as on the *Handbooks* website and in the published volume. A declaration of interests form is not required from Representatives or Observers.

The names and principal affiliations of participants are made available on the website of the *IARC Handbooks of Cancer Prevention* (<http://handbooks.iarc.fr>) approximately 2 months before each meeting. It is not acceptable for Observers or third parties to contact participants before a meeting or to lobby them at any time during the process. Meeting participants are asked to report all such contacts to the IARC Secretariat.

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Working Group Member or an Invited Specialist serves in their capacity as an individual scientist and not as a representative of any organization, government, or industry.

5. Review and evaluation process

A different Working Group is responsible for developing each new volume of the *Handbooks*. Approximately 1 year before the Working Group meeting, the screening intervention to be reviewed is announced on the *Handbooks* website (<http://handbooks.iarc.fr>) and potential participants are selected by IARC staff as described above (Part A, Section 4).

IARC performs literature searches to compile the relevant bibliography in relation to the topic that will be evaluated. Meeting participants are expected to supplement the IARC literature searches with their own searches of published evidence.

The relevant articles are made available to meeting participants, who prepare preliminary

drafts of the sections assigned to them. The participants are provided with instructions on how these drafts should be prepared, in terms of the outline of text and tables, the length, or any other important considerations. The preliminary drafts undergo in-house and external peer review by Working Group Members and Invited Specialists, and the peer-review comments are sent back to the original author, who revises the draft before the meeting.

The Working Group then meets at IARC for eight days to discuss and review all the drafts and to formulate the evaluations. The objectives of the meeting are peer review, evaluation, and consensus. During the first days, the participants meet in separate subgroups to review the drafts of their specific section(s), develop a joint draft, write summaries of the evidence, and propose preliminary evaluations (as appropriate). Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last days, the Working Group meets in plenary session to review the subgroup drafts and develop the final evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

Thus, the tasks of the Working Group are as follows:

1. Ascertain that all appropriate data have been retrieved;
2. Select the data relevant for evaluation on the basis of scientific quality;
3. Prepare summaries of the data that will allow the reader to follow the reasoning of the Working Group;

4. Evaluate separately the efficacy and the effectiveness of the screening procedure(s).

After the meeting, a Special Report is published in the *New England Journal of Medicine* and a summary of the outcome of the meeting is posted on the *Handbooks* website (<http://handbooks.iarc.fr>). Subsequently, the accuracy of the final draft resulting from the meeting is verified by the scientific staff of the *Handbooks* programme, by consulting the original literature, and the volume is edited and prepared for publication. The aim is to publish the full volume within 12 months after the Working Group meeting in both print and digital formats.

6. Inclusion criteria for data for the *Handbooks*

The *Handbooks* do not necessarily summarize or cite the entire body of literature on the intervention being evaluated. Only data considered by the Working Group to be relevant to making the evaluation are included. Epidemiological studies, randomized controlled trials, modelling studies, and meta-analyses published or accepted for publication in the openly available scientific literature are reviewed by the Working Group. The same publication requirement applies to meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B). Also, reports from recognized national or international agencies that have undergone peer review and that are publicly available are considered. Data judged to be uninformative to the evaluation may, at the discretion of the Working Group, be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated (see Part B for details). Meeting abstracts and other reports that do not provide sufficient detail upon which to base an assessment of their quality are not considered. Exceptionally, doctoral theses and other materials that are in their final form and publicly available may be

considered if their inclusion is deemed pertinent to making a final evaluation.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below.

Inclusion of a study does not imply acceptance of the adequacy of the study. Major limitations that impinge on interpretation, or reasons for not giving further consideration to an individual study, are brought to the attention of the reader by the addition of Working Group comments in square brackets.

Studies that are judged to be uninformative to the evaluation are omitted, but the rationale for exclusion should be stated. However, less informative studies may be mentioned briefly when: (i) they provide supporting evidence to that in other studies; or (ii) they provide the only published data available on a specific issue.

The Working Group may conduct additional analyses and use these in their assessment of the evidence. Such analyses are identified by square brackets in the text and tables.

The outline of a *Handbook* on screening includes the following sections.

1. Descriptive epidemiology and disease characteristics

This section succinctly presents data on the cancer being considered: the global distribution and burden, including regional differences and time trends. Expected trends in the absence of screening are a relevant component of this section. The natural history of the disease and the established risk factors and protective factors are briefly described. Information on treatment

and survival in different settings is reviewed, with a worldwide perspective.

2. Screening techniques

Each of the screening techniques to be considered is described in this section. The ability of each procedure to detect cancer and to distinguish cancer from non-cancer conditions is presented:

- Equipment and training to perform the procedure;
- Technical quality control;
- Screening performance, including sensitivity, specificity, or positive predictive value;
- Host factors affecting screening performance.

3. Availability and use of screening practices

An overview of how screening is delivered in different regions of the world is presented in this section, with emphasis on the following aspects:

- Availability of policies and guidelines for screening for that cancer;
- Type of screening provided (opportunistic screening, organized population-wide programme, other screening initiatives); availability of facilities; screening procedures most commonly used or recommended;
- Extent of population coverage and participation rates.

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

4. Efficacy and effectiveness of a screening procedure

For the evaluation of both efficacy and effectiveness, the Working Group considers the following general principles in making judgements about the available studies:

- Relevance of the study;
- Appropriateness of the study design and analysis to the question being asked;
- Adequacy and completeness of the presentation of the results;
- Degree to which chance, bias, and confounding may have affected the results.

4.1 Efficacy

In this section, evidence from randomized controlled trial (RCT) studies is reviewed. All aspects of study design and analysis are critically discussed. Indicators of the efficacy of the procedure in terms of mortality or incidence, as well as other relevant indicators, such as the detectable phases of the natural history of the disease, are presented.

Aspects that are particularly important in evaluating RCTs are: the selection of participants, the nature and adequacy of the randomization procedure, evidence that randomization achieved an adequate balance between the groups, exclusion criteria used before and after randomization, compliance with the intervention in the screened group, and “contamination” of the control. Other considerations include the means by which the outcome (preneoplastic lesions or cancer) was determined and validated (either by screening or by other means of detection of the disease), the length and completeness of follow-up of the groups, and the adequacy of the analysis.

When RCTs are lacking, efficacy cannot be directly evaluated, but only indirectly inferred from observational studies (see below).

4.2 Effectiveness of population-based screening

The impact of the screening procedure when implemented in defined populations is examined in this section.

In this section, mostly observational studies are reviewed, conducted in settings with organized screening programmes or with opportunistic screening. In cohort studies, particular attention is paid to the length and completeness of follow-up; in case-control studies, particular attention is paid to the definition of cases and controls, and the screening method. In all observational studies, the potential for chance, bias, and confounding is carefully examined.

(a) Beneficial effects

Benefits include a decrease in the incidence of invasive cancer or in cancer-related mortality. In addition, indicators used to monitor effectiveness, such as detection rate, rates of interval cancers, and the number of tests performed, may also be considered. Studies of time trends before and after implementation of screening, as well as comparisons, including geographical comparisons, of the occurrence of the disease and death from the disease in populations exposed and not exposed to screening may also be reviewed and interpreted when relevant. In doing this, the Working Group takes into account differences in screening procedures (e.g. frequency and the age of the target population) and of participation rates.

When appropriate, the extent to which improved treatment has been responsible for any observed changes in mortality should be considered in assessing the evidence for effectiveness.

Compliance with participation in screening by a given procedure will also be considered as part of the evaluation of the effectiveness.

(b) Adverse effects

Adverse effects to individuals that are linked to the screening procedure are also reviewed. Evaluation of harms includes estimates of rates of false-positive and false-negative findings and their consequences in screened individuals, overdiagnosis, and interval cancers. Harms may also include screening-related medical complications or discomfort, or psychological effects such as anxiety induced by undergoing screening. The rates of short- and long-term adverse effects of the screening procedure and the likelihood of unnecessary treatment are discussed. Evidence on adverse effects may come from any type of epidemiological study design, including RCTs, observational studies, or other studies as relevant.

(c) Harm–benefit ratio and cost–effectiveness

Evidence for the harm–benefit ratio and the cost–effectiveness of the screening procedure in various settings is considered, mostly from modelling studies. The discussion takes into account the costs per case detected and the benefits per death prevented. Modelling studies will be reviewed similarly to other studies, with particular attention paid to assumptions.

5. Summaries

This section presents summaries of the data reviewed in Sections 1 to 4, providing the key evidence and the rationale leading to the evaluations, as well as important outcomes/findings for which no formal evaluation is conducted. This section is the most read chapter in the entire *Handbook*. For this reason, it is essential that it provides the background and rationale of the Working Group’s evaluation, yet remains concise and understandable to non-specialist readers. The summary should not contain studies or data that are not mentioned in the main text or tables, or that have been considered uninformative by

the Working Group. Technical jargon should be avoided, and no references will be cited in the final version.

In the case of *limited* or *inadequate* evidence, the Working Group should highlight, in the form of a rationale, those aspects of the procedure for which information is lacking and which led to the uncertainty in evaluation.

6. Evaluation

For each screening procedure considered, a separate evaluation of the degree of evidence for efficacy and for effectiveness is formulated according to the following definitions.

It is recognized that the criteria for these evaluations, described below, cannot encompass all factors relevant to an evaluation. In considering all of the relevant scientific evidence, the Working Group may assign the screening procedure to a higher or lower category than a strict interpretation of these criteria would indicate.

- *Sufficient evidence for the efficacy or for the effectiveness of screening by a given procedure* will apply when screening by this procedure is consistently associated with a reduction in mortality from the cancer or a reduction in the incidence of invasive cancer, and chance, bias, and confounding can be ruled out. In addition, for the evaluation of effectiveness, the balance of benefits and harms has been taken into account.
- *Limited evidence for the efficacy or for the effectiveness of screening by a given procedure* will apply when screening by this procedure is associated with a reduction in mortality from the cancer or a reduction in the incidence of invasive cancer, or a reduction in the incidence of clinically advanced cancer, and chance, bias, and confounding cannot be ruled out with reasonable confidence. In addition, for the evaluation of effectiveness,

the balance of benefits and harms has been taken into account.

- *Inadequate evidence for the efficacy or for the effectiveness of screening by a given procedure* will apply when data on incidence or mortality are lacking, or when the number or quality of studies does not permit a conclusion.
- *Sufficient evidence that screening by a given procedure is not efficacious or effective* will apply when any of the following cases hold:
 - o The procedure does not result in earlier diagnosis than in the absence of screening;
 - o The survival of cases detected at screening is no better than that of cases diagnosed routinely without screening;
 - o The screening procedure is consistently associated with no reduction in mortality from or incidence of invasive cancer, and chance, bias, and confounding can be ruled out with reasonable confidence;
 - o There is evidence showing that harms outweigh benefits from the specific intervention.

References

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