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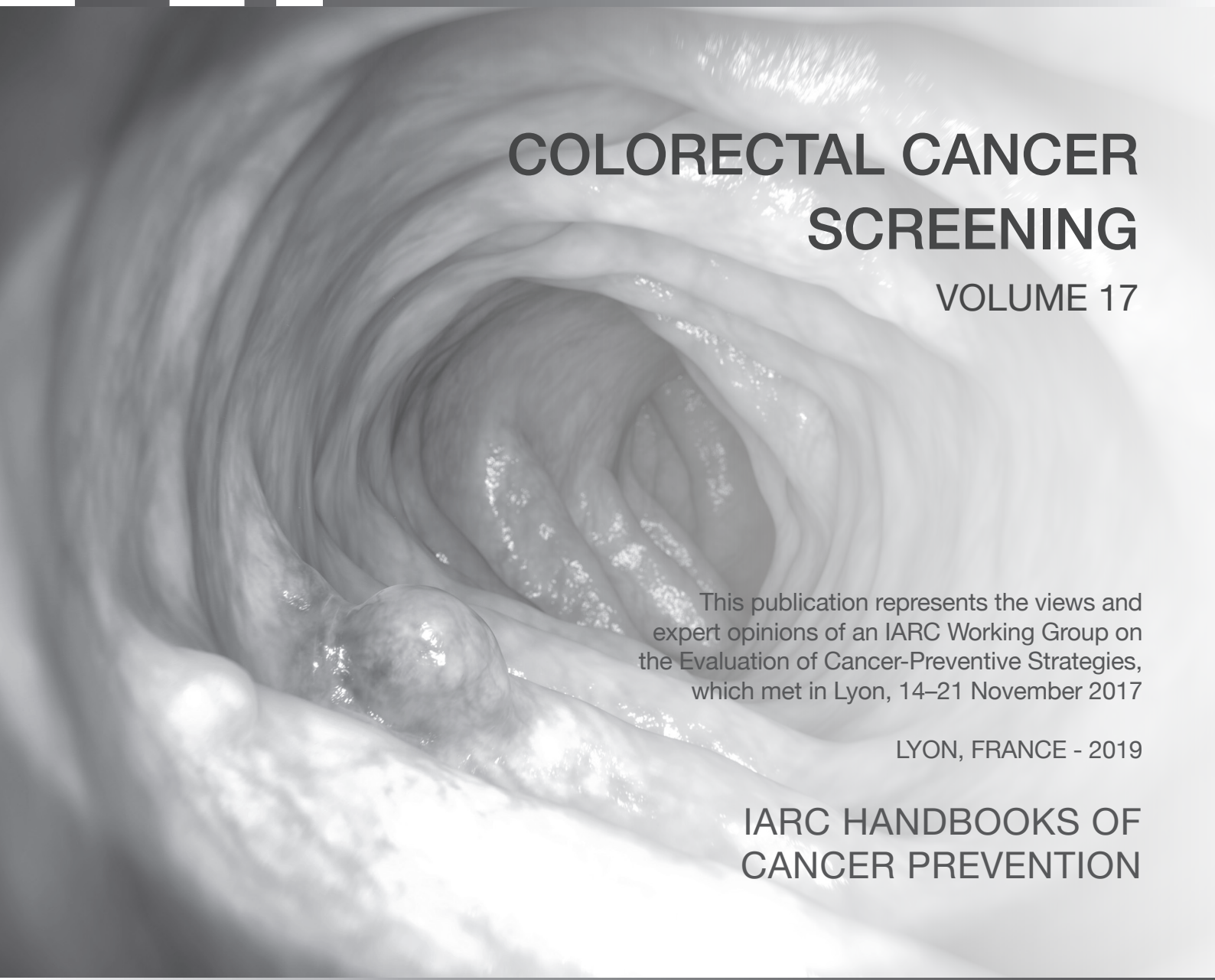

COLORECTAL CANCER SCREENING

VOLUME 17

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Strategies, which met in Lyon, 14–21 November 2017

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IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

GENERAL REMARKS

This seventeenth Volume of the *IARC Handbooks of Cancer Prevention* series evaluates the beneficial and adverse effects of various modalities of colorectal cancer screening. It is the third Volume since the relaunch of the series in 2014.

This Volume of the *IARC Handbooks* is timely, because colorectal cancer screening has not been evaluated in previous *Handbooks*, and there are no World Health Organization recommendations for colorectal cancer screening. In addition, in 2015 the *IARC Monographs* classified processed meat as carcinogenic to humans (Group 1), on the basis of *sufficient evidence* of carcinogenicity in humans: evidence from epidemiological studies that every 50 gram portion of processed meat eaten daily increases the risk of colorectal cancer by 18% (IARC, 2018a).

Colorectal cancer is among the most common cancers worldwide, in both high-income countries and low- and middle-income countries. Primary prevention can be achieved by reducing exposure to preventable risk factors, such as excess body fatness (IARC, 2018b), consumption of alcoholic beverages (IARC, 2012), and tobacco smoking (IARC, 2012), and by increasing physical activity (IARC, 2002); secondary prevention provides important additional options for colorectal cancer control.

Based on a systematic review of the available literature, the Working Group made evaluations of the effectiveness of the different screening modalities reviewed. In addition, the literature was reviewed but no evaluations were made for the screening of individuals at increased risk, for strategies to increase participation in screening programmes, and for emerging techniques other than computed tomography colonography.

The aim of colorectal cancer awareness programmes is to educate individuals about the signs and symptoms of colorectal cancer and the importance of seeking early diagnosis and treatment. Overall, these steps aim to promote the early diagnosis of the disease for better treatment and prognosis and are not considered to be *screening* activities, and therefore such programmes are not included in this review.

While this Volume does not provide public health recommendations regarding implementation of colorectal cancer screening or recommendations for future research, it may serve as the scientific evidence base for implementation of national programmes.

Below are some elements discussed during the Working Group meeting that do not pertain specifically to a screening modality but may enhance the reader's understanding of the topic under review.

Information and awareness

Organized screening programmes, in establishing opportunities for personal contacts with health-care providers for a large number of people, can also provide a unique opportunity

to combine efforts for early detection of cancer with health education interventions aimed at promoting lifestyle changes among asymptomatic individuals, at a time when they may be open to learning about how to reduce cancer risk (van der Aalst et al., 2010). Unhealthy diets, physical inactivity, and smoking are key risk factors for the major noncommunicable diseases, such as cardiovascular diseases, diabetes, and cancer. The available evidence from intervention studies (Robb et al., 2010; Anderson et al., 2014) supports the hypothesis that comprehensive interventions are acceptable for asymptomatic individuals targeted for cancer screening, can favour the adoption of healthier lifestyle habits, and, according to preliminary analyses, may be cost-effective.

Cancer prevention in low- and middle-income countries

In most low- and middle-income countries, a uniform approach for increasing cancer control is challenging at every step of the process. Tailored preventive actions for early detection of cancer must be started concurrently with the development of a reliable health information system and, specifically, with cancer registration. In such settings, early detection strategies and access to treatment for symptomatic individuals are important components of the strategy for reducing cancer-related deaths.

Quality assurance of organized screening programmes

A range of screening strategies for colorectal cancer is currently available, which may show different cost–effectiveness profiles in different settings; in addition, new tests continue to emerge, based on new markers or new imaging modalities. Considering that efficient evaluation of these alternatives within the framework of screening trials presents a challenge, it has been suggested that a good health service programme should integrate the development and testing of new modalities as part of the programme itself, to be able to monitor and assess changes in clinical practice and to provide new evidence on the effectiveness of different options. Screening programmes may then represent the natural platforms for comparative effectiveness research, which could also represent an opportunity to optimize the effectiveness of screening services within existing programmes and to continuously improve their quality. Continuous and systematic monitoring of reliable and evidence-based performance indicators supports quality improvement efforts, providing comparative data as well as new evidence that may inform the adoption of screening strategies or of new tests in population programmes (Bretthauer & Hoff, 2012).

Selection criteria for observational studies on the effects of endoscopic techniques

In reviewing the body of evidence from observational studies of the effectiveness of endoscopic techniques in reducing colorectal cancer incidence and mortality, the Working Group determined strict criteria for inclusion of the available studies. These are the following:

- The study must have been performed in a screening setting.
- There must be a concurrent control group or groups.
- The follow-up must be of adequate length to enable an effect to be observed (> 5 years).
- The intervention must be with contemporary methods (i.e. after 1990).

- There must be a reliable end-point ascertainment.
- The study description must contain information on potential confounders (i.e. colorectal cancer risk factors, competing risks).
- The study design must not exclude prevalent cancer.

Approach for evaluating the effectiveness of emerging techniques

Currently, emerging screening technologies, such as computed tomography colonography, capsule colonoscopy, the multitarget stool DNA test, and blood DNA tests, tend to be evaluated based on performance indicators from a single screening test (typically, sensitivity and specificity), and possibly intermediate end-points associated with colorectal cancer incidence and mortality, i.e. the detection rates of cancer and of advanced adenomas.

To further evaluate the cancer-preventive effects of such technologies, high-quality observational studies could be performed to acquire evidence on cancer incidence and mortality outcomes. Also, randomized controlled trials comparing the emerging technology with one or more conventional screening methods may be undertaken to compare measures of intermediate screening outcomes and/or colorectal cancer incidence and mortality rates. However, the potential for conducting such randomized controlled trials, especially with incidence and mortality end-points, is low because of the high financial and time-related costs. The potential for randomized controlled trials is especially limited if the new technology demonstrates similar, but not substantially better, test performances when compared with conventional screening methods in a tandem study.

Even though observing a mortality reduction remains the most important initial evaluation end-point, when evidence from randomized controlled trials is lacking, once the efficacy of a screening method has been demonstrated with a randomized controlled trial it may be considered reasonable to infer that a new, similar method is efficacious if it can be consistently shown to be similarly effective in the detection of cancer and of precursor lesions (i.e. advanced neoplasia associated with colorectal cancer incidence and mortality). Typically, these intermediate end-points are measured with a prospective tandem design, in which individuals undergo testing with the new technology and then undergo testing with a similar established method as the reference standard. Although the approach has some limitations because of variable performance, performance indicators and detection rates of adenomas and of cancer are compared with those of established screening methods.

Even if the emerging technology is dissimilar to tests previously evaluated by randomized controlled trials (a stool-based test vs a blood-based test, or sigmoidoscopy vs capsule colonoscopy), it is important to carefully consider how the new test could be confidently evaluated with an observational study that compares its performance with that of a reference standard, because all screening tests for colorectal cancer aim to detect early asymptomatic disease in order to reduce cancer incidence and/or mortality. As the pace of innovation increases, these challenges will be increasingly frequent, and there is a growing literature that addresses both the need for and the suggested methodology for timely evaluation of new technologies when randomized controlled trials are not possible or practical (Meijer et al., 2009; Young et al., 2016).

Adenomatous polyps as surrogate biomarkers for primary prevention

Most colorectal cancers develop from adenomatous polyps (adenomas); therefore, people with adenomatous polyps, particularly those arising before age 60 years, are at increased risk of colorectal cancer. The malignant potential of adenomas depends largely on their histological type, grade of dysplasia, and size (Tanaka, 2009).

Removal of adenomas has been shown to reduce the risk of colorectal cancer; prevention of their development has a large potential for preventing colorectal cancer (see Section 3.3.3 for risk reduction by screening).

Recent research has been directed towards the prevention of adenomas and the use of surrogate biomarkers that are altered before polyp formation during colon carcinogenesis (Tanaka, 2009). These surrogate end-point markers could provide a simple and economical tool for preliminary assessment of potentially effective chemopreventive agents for colorectal cancer.

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