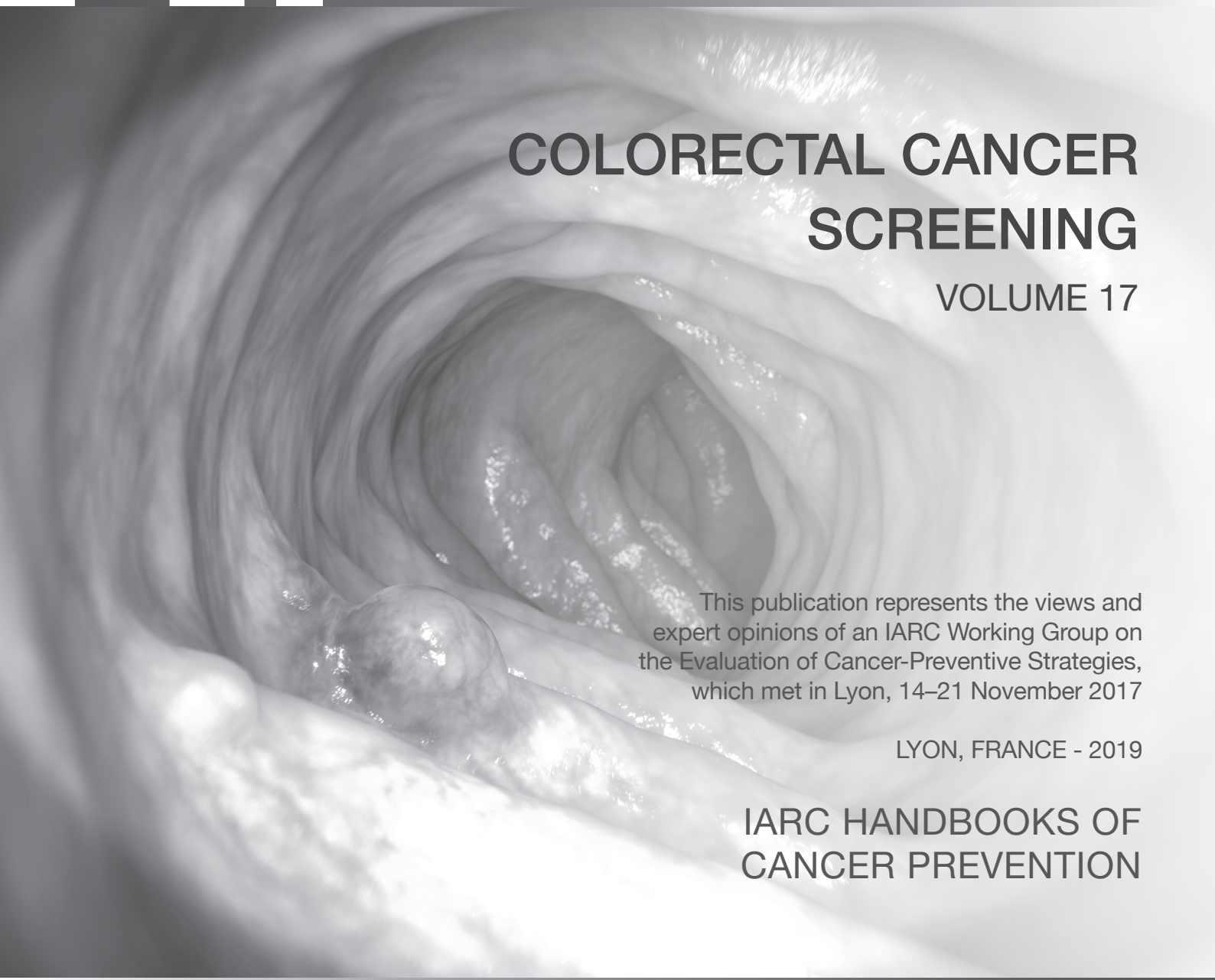
IARC HANDBOOKS



COLORECTAL CANCER SCREENING

VOLUME 17

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IARC HANDBOOKS OF CANCER PREVENTION

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4. SUMMARY

4.1 Colorectal cancer

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide (with an estimated 1.8 million new cases in 2018) and represented more than 10% of the global cancer burden in 2018. There were an estimated 862 000 deaths from CRC in 2018. CRC incidence rates show a strong positive gradient with the level of economic development; the highest rates of CRC are observed in Australia and New Zealand, Europe, and North America, where incidence rates can be 10 times those observed in Africa and parts of Asia. For patients diagnosed in 2010–2014, 5-year net survival was between 60% and 70% in most countries in North America and western Europe, and less than 50% in several countries in Africa, Asia, eastern Europe, and South America, in some of which it was less than 40%. There is variation between countries in the direction and the extent to which incidence and mortality rates are changing over time.

CRC develops mainly from classical adenomas and serrated polyps, which have different molecular backgrounds and give rise to distinct molecular types of CRC. CRC can be classified on the basis of histology, molecular background, and location within the large bowel, and these subtypes vary in clinical characteristics, response to treatment, and outcome. Advanced adenomas have the highest risk of developing into CRC. Precursor lesions can be detected and removed during screening and follow-up colonoscopy.

Stage describes the state of progression of cancer. A large variation in CRC stage is observed worldwide, depending on diagnostic resources, availability of screening, cancer awareness, and health-care organization. Stage at diagnosis is intrinsically linked with outcome: 5-year survival can be as high as 98% for stage I CRC, compared with less than 20% for stage IV CRC in the same setting.

Most CRCs occur sporadically, and a large fraction of the burden is attributable to lifestyle – and potentially modifiable – risk factors of small magnitude. Risk factors for CRC include increased consumption of processed meat, consumption of alcoholic beverages, tobacco smoking, and excess body fatness and abdominal fatness, whereas CRC risk decreases with consumption of dietary fibre, consumption of dairy products, and being physically active. Other risk factors for CRC include non-modifiable host factors such as increasing age, being male, tall stature, and ethnicity. Use of aspirin and other non-steroidal anti-inflammatory drugs effectively reduces the risk of CRC, with duration–risk relationships. However, these medications increase the risk of several diseases and are not recommended for chemoprevention (see Section 4.9.4).

4.2 Colorectal cancer screening worldwide

4.2.1 Europe

In the European Union, the implementation of international cooperative projects contributed to the development of a common framework for the implementation of population-based organized CRC screening programmes. By 2016, population-based organized programmes had been established or piloted in 22 of the 28 European Union Member States. Three European Union countries (Germany, Greece, and Latvia) have opportunistic screening, and Germany is planning to start a population-based programme in 2019. Non-EU countries have less well-developed programmes. Population-based programmes have been started or piloted in 7 of the 19 non-EU countries in Europe (Georgia, Monaco, Montenegro, Norway, San Marino, Serbia, and Switzerland), and opportunistic screening is available in one country (Bosnia and Herzegovina). Most organized programmes have adopted the faecal immunochemical test (FIT) or are in the process of switching from the guaiac faecal occult blood test (gFOBT) to FIT. Colonoscopy is recommended together with FIT in Austria, Germany, and Greece (opportunistic settings). Among countries with population-based programmes, the Czech Republic, Luxembourg, and Switzerland also offer the option to choose between colonoscopy and FIT. Poland is piloting a population-based programme with colonoscopy. Sigmoidoscopy screening has been implemented in two population-based programmes – in England and in Italy (Piedmont) – and in the pilot programme in Norway, in combination with FIT. The European Union guidelines provide evidence-based recommendations on the quality assurance requirements when implementing CRC screening programmes, covering the different phases of the process. Quality assurance initiatives that focus more specifically on the laboratory standards for FIT and on endoscopy services have also been implemented, facilitating national and international comparisons and benchmarking.

4.2.2 Canada and the USA

Screening for CRC was pioneered in the USA; CRC screening in that country is mainly opportunistic, and different modalities (FIT, sigmoidoscopy, colonoscopy, computed tomography colonography, and the multitarget stool DNA test) are recommended by different bodies in different settings. Colonoscopy is the predominant choice. In Canada, a population-based CRC screening programme with gFOBT or FIT has been launched to cover all 10 provinces but not the territories.

4.2.3 Latin America

Of the 21 countries in Central America, South America, and the Spanish-speaking countries of the Caribbean, only Argentina, Brazil, and Chile have population-based pilot CRC screening programmes, in urban areas, with FIT. Six countries (Colombia, Cuba, Ecuador, Mexico, Puerto Rico, and Uruguay) offer opportunistic screening with clinical guidelines, with gFOBT or FIT.

4.2.4 Africa

In African countries, apart from a pilot demonstration research project initiated by IARC/World Health Organization designed to promote voluntary participation in FIT screening in Morocco, no other CRC screening initiative was identified by recent surveys that collected information about current screening activities.

4.2.5 Central, West, and South Asia

In Central, West, and South Asia, population-based organized screening with FIT was implemented in Bahrain (pilot study), Israel,

Kuwait (pilot study), Qatar, and the United Arab Emirates. Opportunistic screening is offered in the Islamic Republic of Iran, Lebanon, Saudi Arabia, and Turkey.

4.2.6 East and South-East Asia

In East Asia, Hong Kong Special Administrative Region (China) (pilot study), the Republic of Korea, and Taiwan (China) have organized screening programmes with FIT. In China, a CRC screening programme was started in 2006, but it has been implemented only in a small proportion of the target population and covers a limited part of the country. In Japan, CRC screening is primarily opportunistic, with some community-based organized programmes.

In South-East Asia, only Singapore has a national screening programme, and Thailand plans to start a national programme in 2018, following the results of a pilot study launched in 2011. Both countries offer FIT screening. Opportunistic screening is offered in Brunei Darussalam, Malaysia, and the Philippines.

4.2.7 Oceania

In Oceania, population-based organized CRC screening programmes are being rolled out in Australia and New Zealand. Both countries have national guidelines, with FIT-based programmes. No organized population-based CRC screening programmes have been implemented in the other countries in the region.

4.3 Stool-based tests for blood

4.3.1 Techniques

Stool-based tests for blood for CRC screening, or faecal occult blood tests (FOBT), can be broadly separated into two methods. The guaiac faecal occult blood test (gFOBT) is an indirect method that detects blood by means of a chemical reaction based on the peroxidase activity of haemoglobin that reacts with paper impregnated with guaiac. The faecal immunochemical test (FIT) is a method based on a specific antigen–antibody reaction where the antibody binds exclusively to human haemoglobin.

gFOBT does not exclusively detect human haemoglobin, and therefore other sources of peroxidase activity, such as raw or half-cooked meat or some uncooked vegetables, could lead to a positive result. In contrast, antioxidants in drugs or foods (e.g. vitamin C) block the peroxidase reaction, potentially leading to a negative test result. gFOBT can be analysed with or without rehydration. In general, gFOBT does not detect faecal haemoglobin concentrations of less than approximately 600 µg Hb/g faeces, although the analytical sensitivity is higher when gFOBT is rehydrated or with the newer high-sensitivity gFOBT. The clinical sensitivity of a single gFOBT (of any type) is in the range of 16–31% for the detection of advanced neoplasia and 25–38% for CRC, and the average specificity for CRC is 98%.

FIT detects colonic human blood with high analytical sensitivity. It is available in a qualitative form (based on immunochromatography) or in a quantitative form (based on immunoturbidimetry). In general, compared with gFOBT, FIT detects lower levels of faecal haemoglobin at concentrations ranging from 1 µg to 300 µg haemoglobin/g faeces, depending on the manufacturer. The sensitivity of a single FIT is in the range of 27–67% for the detection of advanced neoplasia and 61–91% for CRC, and the specificity ranges from 91% to 98%, depending on the cut-off values and FIT strategies used.

4.3.2 Randomized controlled trials of screening with gFOBT

Four individually randomized trials of annual or biennial gFOBT screening with individual randomization in populations at average risk aged 45–80 years and conducted in different countries have shown significant reductions in

CRC mortality (relative risk [RR] for invitation ranging from 0.68 to 0.91: corrected RR for participation ranging from 0.65 to 0.82), after 9–30 years of follow-up. One of the meta-analyses, published in 2006, which included only the biennial gFOBT screening arms of three of the randomized controlled trials (RCTs), showed a significant reduction of 13% in CRC mortality associated with invitation to screening, whereas the other three meta-analyses of four RCTs, which included the single RCT conducted in the USA with an annual screening arm, reported a reduction of 16–18% in CRC mortality.

The one RCT that used gFOBT with rehydration in most samples and had extended follow-up, conducted in the USA, observed a reduction in CRC incidence of 20% (95% confidence interval [CI], 0.70–0.90) for annual screening and 17% (95% CI, 0.73–0.94) for biennial screening, after 18 years of follow-up in individuals aged 50–80 years.

There is no published evidence from individually randomized trials on the efficacy of FIT screening in reducing CRC mortality or incidence in screening populations at average risk.

4.3.3 Observational studies on preventive effects of stool-based tests for blood

(a) gFOBT screening and reduction in colorectal cancer mortality and incidence

A total of five cohort studies and five case–control studies of gFOBT conducted in screening settings in different geographical regions reported on CRC mortality and/or incidence. The two larger cohort studies of biennial gFOBT without rehydration, with 10–21 years of follow-up, showed reductions in CRC mortality of 10–13%, which remained significant in all scenarios after adjusting for screening participation. Four case–control studies conducted in the USA and in Europe reported a reduction in CRC mortality of 40% on average when comparing screened versus non-screened individuals, although this could be overestimated because of inherent limitations of the study design. A recent meta-analysis based on 17 studies in a screening setting showed an overall significant reduction of 18% in CRC mortality in relation to gFOBT screening (any interval), with similar results in separate analyses of observational studies and of RCTs.

Overall, the available evidence did not point towards a consistent reduction in CRC incidence with gFOBT screening. Only one of three cohort studies, reporting on CRC incidence in Denmark, found a significant reduction after approximately 3.5 years of gFOBT screening without rehydration, and the magnitude of the reduction in CRC incidence was only 6% when comparing screened versus non-screened individuals of the same age.

(b) FIT screening and reduction in colorectal cancer mortality and incidence

The body of evidence for FIT screening and CRC mortality and incidence is small, but the findings are consistent throughout.

Two large cohort studies conducted in Italy, with 8 years and 15 years of follow-up and four or more rounds of biennial FIT screening in individuals aged 50–70 years, and one study in Taiwan, China, with biennial FIT screening and shorter follow-up, all reported significant reductions of up to 40% in CRC mortality. In addition, one case–control study in Japan with annual FIT screening observed substantial CRC mortality reduction up to 2 years after the last screen. One ecological study in Italy, comparing two similar geographical areas with early screening (three or four rounds) versus late screening (one round) with biennial FIT and adjusting for age and sex, provided evidence of CRC mortality reduction in the group screened for a longer period.

Significant reductions in CRC incidence of 10% and 22% were reported in the two Italian cohort studies after 8 years and 15 years of follow-up, respectively. In addition, one ecological study conducted in Italy provided some indication of reduced CRC incidence after

20–24 years of follow-up only in the area that had started with screening earlier, screened biennially for eight rounds with gFOBT, and for five rounds with FIT thereafter.

4.3.4 Adverse effects of screening with stool-based tests for blood

The most commonly reported harms in relation to screening with stool-based tests for blood are psychological consequences as a result of screening per se. One trial showed no significant difference between psychiatric morbidity or suicide rates before and after gFOBT screening. Several studies showed moderate to high anxiety after a positive screening result, but this returns to pre-screening levels immediately after a subsequent negative screening result (either a second gFOBT or a colonoscopy). No associations were observed between an inappropriate reaction (e.g. ignoring subsequent cancer symptoms) after a negative gFOBT screening result and delayed diagnosis. CRC detected after a negative screening result (an interval cancer) had earlier stage at diagnosis than CRC detected in non-screened individuals, but later stage at diagnosis than screen-detected CRC. There are no reports of physical harms directly associated with FOBT screening. There are rare serious harms from colonoscopy or sigmoidoscopy used to evaluate individuals with a positive screening result from a stool-based test for blood. These include bleeding, perforation of the colon, and other serious complications leading to hospitalization. They occur in less than 1 in 10 000 FOBT screens in populations at average risk. Based on the four RCTs, there is no net overdiagnosis associated with gFOBT screening, given that the cumulative incidence of CRC in the screening arm was very similar to or lower than that in the control arm.

4.3.5 Benefit–harm ratio and cost–effectiveness of screening with stool-based tests for blood

CRC screening with gFOBT or FIT provides gains in quality-adjusted life years compared with no screening. Screening annually with higher-sensitivity gFOBT or FIT leads to higher quality-adjusted life years gained than screening biennially but requires more screening resources. Furthermore, costs per quality-adjusted life year gained were less than US$ 30 000 with FOBT screening, even showing cost savings compared with no screening. The cost–effectiveness of CRC screening with stool-based tests for blood has been evaluated across the world, with reports from Asia, Europe, and North America showing benefit with acceptable levels of cost. The cost estimates showed wide variability, owing to the variation in costs between countries; therefore, the cost per life year gained from different studies can only be compared qualitatively.

4.4 Endoscopic methods

4.4.1 Techniques

Sigmoidoscopy and colonoscopy are the two endoscopic techniques used for CRC screening. Their primary screening goal is the detection of early cancer and precancerous polyps.

The requirements for endoscopic procedures include a trained endoscopist (physician or non-physician), endoscopic equipment, support staff for biopsies and similar procedures, and provisions for patient comfort (physical setting and sedation, as appropriate).

Substantial data exist on performance and training for both physician and non-physician endoscopists. Several competency standards and quality measures are recommended for lower gastrointestinal endoscopy. Different skill levels are required for different procedures, and skill levels vary substantially by setting; proposed

skill criteria for each examination exist for international standardization. A recent European guideline noted 44 different performance measures, many of which evaluate processes (e.g. documentation of certain findings) rather than evidence-based factors that influence outcomes. Additional recommendations exist for particular techniques, such as endoscopic polypectomy and endoscopic mucosal resection. The primary screening performance quality metrics for endoscopic screening are completion of the examination to the minimum desired extent (typically the junction of the sigmoid and the descending colon for sigmoidoscopy and the caecum for colonoscopy), adequacy of bowel preparation, and thoroughness of the endoscopic inspection (adenoma detection rate).

4.4.2 Randomized controlled trials of screening with sigmoidoscopy

Four large RCTs of sigmoidoscopy screening have been performed, in Italy, Norway, the United Kingdom, and the USA. All four trials were initiated in the 1990s. The RCTs ranged in size from approximately 34 000 subjects to 170 000 subjects. The three trials in Europe had once-only screening, and the trial in the USA had two rounds of screening; the median follow-up was about 11 years for all the trials. The RCTs consistently showed reductions in risk of CRC incidence and mortality, with relative risks in the range of 0.77–0.82 for CRC incidence and 0.69–0.78 for CRC mortality. All of the results for incidence were statistically significant, and all but one of the results for mortality were significant. An extended follow-up of one trial, with a median follow-up of 17 years, showed a persistent CRC incidence and mortality benefit, with relative risks of 0.74 for incidence and 0.70 for mortality.

In the meta-analyses of the four RCTs reported, the meta-relative risks were in the range of 0.78–0.79 for incidence and 0.72–0.74 for mortality. When stratified by anatomical location, the risk reduction was more substantial for distal CRC than for proximal CRC and was significant only for distal CRC (RR, 0.71 for incidence and 0.63 for mortality). In a pooled analysis of three RCTs that stratified by sex, the risk reduction was significant for both men and women, for both incidence and mortality.

A meta-analysis of the four RCTs found a small reduction in all-cause mortality (RR, 0.97; 95% CI, 0.96–0.99).

4.4.3 Observational studies on preventive effects of endoscopy

There are few large high-quality observational studies that have evaluated the preventive effects of endoscopy in population-based screening programmes. Only those studies that were conducted in a screening setting and that did not exclude prevalent cancers at baseline were included.

(a) Sigmoidoscopy screening and reduction in colorectal cancer incidence and mortality

The most recent meta-analysis of the effectiveness of sigmoidoscopy screening included two cohort studies and seven case–control studies published in 1992–2013. The estimated risk reduction for CRC incidence with sigmoidoscopy screening was 49% (RR, 0.51; 95% CI, 0.39–0.65) (based on five studies). The risk reduction was larger for distal CRC than for proximal CRC (five studies).

The estimated risk reduction for CRC mortality with sigmoidoscopy screening was 47% (RR, 0.53; 95% CI, 0.30–0.97) (based on three studies), with a mortality reduction of 66% for distal CRC but no significant mortality reduction for proximal CRC (four studies). These risk reductions for overall CRC and for distal CRC are comparable to those from the adjusted per-protocol analyses from the RCTs. One more recent large case–control study found mortality reductions for overall CRC (36%) and both

distal CRC (48%) and proximal CRC (25%) after 10 years of follow-up.

(b) Colonoscopy screening and reduction in colorectal cancer incidence and mortality

The most recent meta-analysis of observational studies of the effectiveness of colonoscopy screening included three cohort studies and three case–control studies published in 2005–2014. The estimated risk reduction for CRC incidence with colonoscopy screening was 69% (RR, 0.31; 95% CI, 0.12–0.77) (based on five studies). An additional large case–control study, published after this meta-analysis, found significant incidence reductions for overall CRC (43%) and both distal CRC (55%) and proximal CRC (35%).

The estimated risk reduction for CRC mortality with colonoscopy screening was 68% (RR, 0.32; 95% CI, 0.23–0.43) in the meta-analysis (based on three studies); the results of subsequent studies (one cohort study and one case–control study) concurred with these findings. A recent large case–control study found significant mortality reductions for both distal CRC (75%) and proximal CRC (65%) after 10 years of follow-up.

4.4.4 Adverse effects of screening with endoscopic techniques

The proportion of individuals who undergo a screening sigmoidoscopy that results in a follow-up colonoscopy and who will ultimately not be diagnosed with any cancerous or precancerous lesions (false-positive results) is not well reported in studies. The percentages of patients referred for colonoscopy after sigmoidoscopy in the RCTs ranged from 5% to 23%, depending on referral criteria. False-positive results are not an issue for primary colonoscopy screening, in which, if it is appropriate, polyps can be removed during the screening procedure and no further assessment is required.

The proportion of overdiagnosis of CRC from endoscopy screening is uncertain, because it is not possible to disentangle overdiagnosis from the preventive effect of endoscopy screening. Because endoscopy screening has been demonstrated to significantly reduce CRC incidence, the rate of overdiagnosis is smaller than the preventive effect of endoscopy screening. Overtreatment of precancerous lesions is considerable, but the harm is modest.

Complications in CRC screening with sigmoidoscopy or colonoscopy that are defined as serious include death within 30 days and hospitalization within 30 days because of serious bleeding or perforation. For colonoscopy, perforation rates in two of the trials currently under way were 0.08–0.2 per 1000 procedures. In the two trials and three meta-analyses of population-based studies, bleeding rates were 0.8–2.4 per 1000 procedures.

Compared with colonoscopy, sigmoidoscopy has fewer adverse effects, requires less bowel preparation, and poses a lower risk of bowel perforation. In a population at average risk, perforations from sigmoidoscopy were relatively uncommon (0.1 per 1000 procedures), as were episodes of major bleeding (0.2 per 1000 procedures). The patient factors associated with endoscopy-related major bleeding or perforation were increased age and having a polypectomy.

On the basis of a few large-scale studies, the mortality rate within 30 days associated with endoscopic procedures was estimated to be 1 in 15 000.

The risks of less serious complications are less well documented. The few studies on the psychological consequences in individuals who were not found to have an advanced neoplasia at sigmoidoscopy have suggested that these effects, if any, are transient.

4.4.5 Benefit–harm ratio of screening with endoscopic techniques

To assess the benefit–harm ratio, the systematic review and decision analysis of the United States Preventive Services Task Force estimated that repeated colonoscopy at ages 50 years, 60 years, and 70 years could result in 250–275 life years gained per 1000 individuals aged 40 years requiring an average of just more than four colonoscopies in a lifetime (including surveillance colonoscopies), corresponding to 14.5–16.5 colonoscopies per life year gained.

Modelling studies estimated the quality-adjusted life years gained with screening to be positive, consistently demonstrating that the benefits of endoscopy screening outweigh its harms, with an estimated net benefit of endoscopy screening in the range of 50–125 quality-adjusted life years per 1000 individuals screened starting at age 50 years. Estimates for disability-adjusted life years averted were also consistently positive; these were lower than the estimated quality-adjusted life years gained, but the populations were not comparable between the analyses.

Most modelling studies showed that CRC screening with either colonoscopy or sigmoidoscopy is cost-effective across different willingness-to-pay thresholds. The studies assumed that screening started no earlier than age 40 years and stopped no later than age 80 years. The results from studies that addressed the optimal age at which to start or stop screening, or the optimal screening interval, were inconsistent.

Modelling estimates are based largely on data from settings with high CRC incidence and high income. Therefore, the results of these studies may not easily be transferable to other settings.

4.5 Comparison of the preventive effects of endoscopic methods and stool-based tests for blood

4.5.1 Reduction in colorectal cancer incidence or mortality

The most recent update of an indirect meta-analysis of RCTs comparing CRC screening strategies suggested that sigmoidoscopy is more effective than gFOBT in reducing CRC incidence (RR, 0.84; 95% predictive interval, 0.72–0.97) but not CRC mortality (RR, 0.89; 95% predictive interval, 0.68–1.17). Of note, the meta-analysis did not take into account the most recent updates of the sigmoidoscopy RCTs.

Another indirect meta-analysis, including RCTs and observational studies in a screening setting, suggested that colonoscopy may be more effective than both sigmoidoscopy (RR, 0.56; 95% CI, 0.32–0.94) and gFOBT (RR, 0.49; 95% CI, 0.30–0.76) in reducing CRC mortality.

4.5.2 Detection rates of adenoma and colorectal cancer

Two meta-analyses of RCTs compared the detection rates of advanced neoplasia, advanced adenoma, or CRC across screening modalities. One of the meta-analyses reported that endoscopic techniques (colonoscopy and sigmoidoscopy) had higher detection rates than stool-based tests for blood (gFOBT or FIT) for both advanced neoplasia (RR, 3.21; 95% CI, 2.38–4.32) and CRC (RR, 1.58; 95% CI, 0.97–2.56). The other meta-analysis showed that screening with sigmoidoscopy (alone or in combination with stool-based testing for blood) was more effective than stool-based testing for blood alone in detecting advanced adenoma and CRC. Specifically, the detection rates of advanced adenoma with sigmoidoscopy (alone or in combination with stool-based testing for blood) were on average about 7 times those with one-time gFOBT (RR, 7.23; 95% CI,

4.86–10.75) and about 4 times those with FIT (RR, 3.74; 95% CI, 3.03–4.62).

The results of two subsequent RCTs, conducted in Spain and Italy, were consistent with the observation of higher detection rates of advanced neoplasia and advanced adenoma with endoscopic techniques compared with stool-based tests for blood. In addition, the trial in Spain showed that sigmoidoscopy (simulated from colonoscopy data considering only lesions detected in the rectum and sigmoid colon) was better than one-time FIT in detecting distal neoplasia and that sigmoidoscopy and FIT had a similar performance in detecting advanced proximal neoplasia.

4.5.3 Cost–effectiveness

One systematic review on the cost–effectiveness of CRC screening compared the cost–effectiveness of endoscopic techniques with those of stool-based tests for blood. All of the models included consistently showed that both 10-yearly colonoscopy and 5-yearly sigmoidoscopy are more cost-effective than annual gFOBT. Six models found colonoscopy to be more cost-effective than annual FIT, whereas three models showed FIT to be more cost-effective than colonoscopy. Thirteen studies compared annual FIT with 5-yearly sigmoidoscopy, and all of them found FIT to be more effective and less costly.

4.6 Computed tomography colonography

The technology of computed tomography (CT) colonography provides two-dimensional and three-dimensional images of the colon with a non-invasive method. The colon needs to be prepared before the examination and distended during the examination with air or carbon dioxide inserted through a small, flexible catheter. Recently, faecal tagging has facilitated the development of colon preparation protocols with a reduced dose of a conventional cathartic agent or even without such an agent.

Based on four high-quality tandem studies of asymptomatic individuals, CT colonography is less sensitive than colonoscopy for the detection of small adenomas and polyps and has sensitivity nearly equivalent to that of colonoscopy for lesions 10 mm or larger, although there is variation between studies; this difference in sensitivity disappeared after adjustment for participation rate.

Three RCTs conducted in screening settings in Europe assessed participation rates and detection rates for lesions compared with other screening modalities, namely colonoscopy, sigmoidoscopy, and FIT. In the RCT in the Netherlands, compared with colonoscopy, CT colonography had an equivalent detection rate of cancer (0.5% for both), a lower detection rate of advanced adenomas (5.6% vs 8.2%), and a lower detection rate of adenomas 10 mm or larger (5.4% vs 6.3%). In one of the RCTs in Italy, the detection rates of advanced neoplasia were similar between CT colonography and sigmoidoscopy (5.1% vs 4.7%). In the RCT in Italy that compared CT colonography with FIT, CT colonography detected more CRC compared with FIT (0.5 vs 0.1) and more advanced adenomas (4.7% vs 1.6%) per participant.

In the analyses of three microsimulation models that all assumed 100% participation in screening, the estimated median reduction in the lifetime risk of dying from CRC associated with screening between age 50 years and age 75 years was similar between CT colonography every 5 years, annual FIT, annual FIT plus sigmoidoscopy every 10 years, and colonoscopy every 10 years.

Harms associated with CT colonography include perforation (for which the risk is very low compared with that of colonoscopy), radiation-induced cancer, the downstream effects of detection of extracolonic findings that warrant

further investigation, and the potential harms of follow-up colonoscopy after a positive test.

When the cost–effectiveness of CT colonography is considered relative to no screening, CT colonography screening consistently meets conventional criteria for cost–effectiveness. Comparative cost–effectiveness estimates are influenced by assumptions about CT colonography costs and participation rates, for which only limited information is available.

4.7 Participation in screening for colorectal cancer

4.7.1 Determinants of participation in colorectal cancer screening

Participation in screening for CRC is influenced by several factors that interact at the policy, organization, provider, and patient levels.

Insurance status and access to primary care are very important determinants of screening participation. Factors related to the organization of screening that have been shown to have an impact on participation include scheduling screening appointments, active call-and-recall systems, the amount of time required to perform screening, and the distance of the subject's residence from the test provider. At the provider level, determinants of participation include the involvement of general practitioners, the use of informational material, time dedicated to preventive care, and knowledge about the effectiveness of the screening modalities. A specific barrier to participation in CRC screening in the general population is dislike of the available tests; also, there is evidence of differential participation by sex for stool-based tests for blood and endoscopy. In both men and women, participation tends to be lower for colonoscopy than for sigmoidoscopy or stool-based tests for blood.

The following have been identified as other factors that influence an individual's likelihood of participating in CRC screening: lack of awareness of CRC and of the purposes of CRC screening; perceived susceptibility to CRC; lack of knowledge about screening effectiveness and procedures; fatalistic beliefs about CRC; negative attitudes towards preventive interventions; and perceptions about the relative weights of short-term inconveniences and long-term benefits. These factors are likely to mediate the association of socioeconomic status and education level with participation in CRC screening. Education level (including language barriers), access to care, and level of knowledge also contribute to the observed differences in participation between ethnic groups. Other factors that were found to strongly influence participation are anxiety associated with repeated testing and the level of support provided by the primary care physician and by a partner.

4.7.2 Approaches to increase participation in colorectal cancer screening

The introduction of population-based organized CRC screening programmes is the preferred option to increase participation in screening, by providing a context in which participation in screening and related assessments is not limited by financial or other organizational barriers, and therefore favours the reduction of inequities in screening access.

4.7.3 Interventions to increase participation in endoscopy screening

Eleven randomized trials have assessed interventions to increase participation in endoscopy screening (colonoscopy or sigmoidoscopy). Interventions such as patient navigation, management, coaching, or counselling (four RCTs) had a significant positive effect in some studies but not in others. Interventions in the form of informational brochures compared with usual care (two RCTs) or tailored invitation letters compared with standard invitation letters (four

RCTs) had a modest impact on increasing participation. A study assessing the use of advance notification letters found a positive impact on increasing participation. In one trial, the addition of a discussion with the general practitioner to providing an informational leaflet had no significant effect.

4.7.4 Interventions to increase participation in screening with stool-based tests for blood

More than 25 randomized trials to assess interventions to increase participation in screening with stool-based tests for blood have been conducted in asymptomatic individuals at average risk of CRC in high-income countries (Australia, Israel, and countries in North America and western Europe). The following interventions were all found to have a modest effect on increasing participation: advance notification letter; postal mailing of kits; written, telephone, and text message reminders; telephone contact with an advisor; invitation letter signed by a general practitioner; training of general practitioners focused on communication skills; and reminder letters sent to general practitioners.

4.7.5 Comparison of participation in two screening methods

Several comparative trials conducted in screening settings and two meta-analyses of such trials compared the participation rates with different screening methods, alone or in combination. Overall, participation rates were higher with FIT than with gFOBT, and the adoption of FIT in population-based programmes resulted in a reduction in disparities in access to CRC screening. In several RCTs, participation was lower with endoscopy screening than with stool-based tests for blood, although these comparisons were based on a single invitation round for stool-based tests for blood. In two trials, conducted in Australia and Italy, no increase in participation in CRC screening was observed when invitees where offered a choice of tests for CRC screening. A large population-based study found that the sequential offer of screening with sigmoidoscopy followed by FIT (i.e. people who refused sigmoidoscopy were invited for FIT) can increase overall participation, although participation was still lower than when FIT was offered alone.

4.8 Emerging techniques

Emerging technologies may be based on structural examinations that enable visual investigation of the entire colon, such as capsule colonoscopy, and examinations based on an analysis of biomarkers in stool, blood, or breath, such as volatile organic compounds (in breath), and of various protein, RNA, and DNA markers. Currently, three technologies have had at least some large-scale evaluation in populations at average risk compared with an established screening modality: the multitarget stool DNA test, capsule colonoscopy, and the methylated *Septin* 9 (*mSEPT9*) blood DNA test. All of these tests require a follow-up colonoscopy after a positive result, which entails the known reported adverse effects of colonoscopy (see Section 4.4).

4.8.1 Stool-based tests

Currently, one test is commercially available that is based in part on detection of mutations in tumour DNA found in stool: the multitarget stool DNA test. Specific targets of the multitarget stool DNA test include *KRAS* point mutations and aberrantly methylated *NDRG4* and *BMP3*. The multitarget stool DNA test also includes an immunoassay component (see Section 4.3). The test result is determined to be positive or negative on the basis of a combined quantitative assessment of individual components of the test.

In a large screening population in which all individuals underwent screening with colonoscopy, FIT, and the multitarget stool DNA test, the multitarget stool DNA test detected significantly more cancers and advanced neoplasia compared with FIT, but showed a lower specificity for non-advanced lesions.

Modelling studies suggest that the multitarget stool DNA test is generally not cost-effective, because of high costs compared with simpler stool-based tests such as FIT.

4.8.2 Capsule colonoscopy

After extensive bowel preparation, the patient swallows a video capsule while wearing a data recorder. As the capsule transitions through the gastrointestinal tract, images are captured from two cameras, one at each end of the device. Patients found to have important lesions will require follow-up colonoscopy for further investigation. Capsule colonoscopy is approved for screening in the USA.

In a single large-scale tandem study with colonoscopy, capsule colonoscopy identified individuals with one or more polyps 6 mm or larger with a sensitivity of 81% (95% CI, 77–84%) and a specificity of 93% (95% CI, 91–95%).

4.8.3 Blood-based tests

There is currently a single commercially available test that is based on the detection of tumour DNA in blood: the *mSEPT9* DNA test. As with the multitarget stool DNA test, the results provided are either positive or negative. The *mSEPT9* DNA test is approved for screening in China and the USA.

In a large prospective study, the sensitivity of the *mSEPT9* DNA test for CRC was 48.2% and the specificity was 91.5%, with a higher sensitivity for the detection of more advanced lesions.

4.9 Populations at high risk of colorectal cancer

Individuals at high risk of CRC fall into four categories of risk factors: genetic predisposition, family history of colorectal neoplasia, personal history of colorectal neoplasia, and medical conditions that predispose to CRC. Because individuals at high risk require more intensive testing, the term "surveillance" is generally used, and the term "screening" is reserved for asymptomatic populations at average risk. However, the evidence of a preventive effect of surveillance in these populations at high risk is at best limited.

4.9.1 Genetic predisposition

Genetic predisposition, which accounts for about 5% of all CRCs, can be subdivided into non-polyposis syndromes, adenomatous polyposis syndromes, and non-adenomatous polyposis syndromes. Non-polyposis syndromes include Lynch syndrome, which is caused by mismatch repair deficiency, and familial CRC, which is a genetically heterogeneous group. The most common adenomatous polyposis syndrome is familial adenomatous polyposis, which is caused by mutations in the *APC* gene, but there are also several rare genetically determined adenomatous polyposis syndromes. Non-adenomatous polyposis syndromes fall into two groups: (i) hamartomatous polyposis syndromes, which include Peutz–Jeghers syndrome, Cowden syndrome, and juvenile polyposis syndrome, and (ii) serrated polyposis syndrome.

Overall, there is little evidence on which to base decisions about surveillance strategies for individuals with genetic predisposition. For individuals with non-polyposis syndromes, colonoscopy is usually recommended every 1–2 years starting at age 20–25 years, and this is the only intervention in populations at high risk that has been proven to be effective. With familial adenomatous polyposis, the

surveillance strategy is dependent on the severity of the condition. For classic familial adenomatous polyposis, annual sigmoidoscopy is recommended from age 11 years, changing to colonoscopy when adenomas start to appear. For attenuated familial adenomatous polyposis, colonoscopy every 2 years is recommended from age 20 years, because proximal adenomas in the absence of distal lesions are common. For the rarer adenomatous polyposis syndromes, colonoscopy every 2 years is generally accepted as being appropriate. For hamartomatous (non-adenomatous) polyposis syndromes, colonoscopy is recommended every 2 years, from age 25 years for Peutz–Jeghers syndrome and from age 15 years for juvenile polyposis syndrome. No definitive guidance for surveillance is available for Cowden syndrome. For serrated polyposis syndrome, colonoscopy every 2 years from the time of diagnosis is recommended, but this strategy may be modified according to the histological classification of the lesions.

4.9.2 Family history of colorectal neoplasia

A family history of CRC is a well-established risk factor for developing CRC, but the relative importance of the underlying factors (i.e. genetic predisposition and shared environmental factors) is unclear. In people with a first-degree relative with CRC, the risk of CRC is approximately 2 times that in people with no such family history; the risk of CRC can increase up to 4-fold, depending on the number of relatives affected with CRC or advanced adenomas and the age at diagnosis.

Evidence is scarce for the effectiveness of surveillance and for the determination of surveillance intervals in individuals with a family history of CRC. Surveillance strategies, including surveillance intervals, vary by country and setting.

4.9.3 Personal history of colorectal neoplasia

Precancerous lesions detected at colonos copy are removed as a preventive measure during screening. However, patients diagnosed with precancerous lesions have a higher risk of developing subsequent advanced adenomas or CRC, compared with people with no such findings. The magnitude of the risk and the recommended surveillance intervals depend largely on the characteristics of the lesions and the number of lesions, which are used to distinguish between patients with high-risk characteristics and those with low-risk characteristics.

Evidence on the effectiveness of surveillance after the detection of serrated lesions and polyps is limited. Recent guidelines recommend surveillance colonoscopy after 3 years after the detection and removal of high-risk sessile serrated polyps and lesions and traditional serrated adenomas, and after 5 years after the detection of low-risk sessile serrated polyps and lesions.

4.9.4 Medical conditions

Patients with certain medical conditions, including inflammatory bowel disease, acromegaly, ureterosigmoidostomy, and cystic fibrosis, have a significantly increased risk of CRC, and require an increased surveillance strategy compared with that for populations at average risk.