Controversies in Colorectal Cancer Screening

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Key Words

Colorectal cancer · Colorectal cancer screening · Faecal occult blood tests

Abstract

Background: Colorectal cancer (CRC) is one of the most common cancers worldwide and a good candidate for screening programmes. However, there is controversy concerning which of the available screening tests should be used. **Summary:** There is general agreement that screening for CRC in the asymptomatic population should begin at the age of 50. Several different screening methods are available which can be separated into those that mainly detect cancers: faecal occult blood tests [guaiac (FOBT) and immunochemical (FIT)], genetic stool tests, blood tests and the M2-pyruvate kinase (M2-PK) test. Methods that detect cancers and polyps are colonoscopy, sigmoidoscopy, CT-colonography (CT-C) and colon capsule endoscopy. The only tests for which a reduction in CRC mortality compared to no screening have been proven in randomized trials are FOBT and sigmoidoscopy. Several trials suggest that FIT are superior to FOBT in terms of detection rates of cancers and advanced adenomas and possibly compliance. There is indirect evidence suggesting efficacy of colonoscopy as a screening test. The role of CT-C is controversial. There is data suggesting a good sensitivity for neoplasia >9 mm with a lower sen-

sitivity for smaller neoplasia. However, radiation exposure is considered a major limitation in some countries. Unresolved questions include the lesion cut-off for referral to colonoscopy and work-up of extracolonic findings. For other methods, like genetic stool testing using newer markers, blood tests, capsule endoscopy and M2-PK, there is currently insufficient data on screening of the asymptomatic population.

Key Messages: Colorectal screening is recommended and should be performed in the form of an organized programme. If detection of early-stage cancers is the aim of a screening programme, FIT seem to be superior to FOBT. If detection and removal of adenomas is the aim of a screening programme, endoscopic methods seem to be good alternatives. Sigmoidoscopy is easier to perform but will likely only have an effect on distal cancers. Colonoscopy is more invasive but enables inspection of the whole colon. The role of CT-C, capsule endoscopy, genetic stool tests, blood tests and M2-PK is currently unknown.

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Colorectal cancer (CRC) is one of the most common cancers worldwide. In 2012 about 1.3 million new cases were diagnosed with CRC and nearly 700,000 patients died of the disease (Globoscan 2012). CRC has several characteristics that make it a good candidate for screening programmes. If diagnosed at an early stage the prog-

nosis is good. Furthermore, the majority of cancers develop slowly from adenomatous precursors, the removal of which can prevent cancers. Due to epidemiologic data there is general agreement that screening in the asymptomatic population should begin at the age of 50. Several methods are available for screening which will be discussed in this review. Screening will have the maximum effect if it is done in the form of an organized programme with regular monitoring of screening outcomes.

Screening methods can be classified into those that mostly detect cancers and those that are also able to detect polyps. Methods that primarily detect cancers include faecal occult blood testing and genetic stool and blood tests as well as the M2-pyruvate kinase (M2-PK) test. Methods that detect cancers and polyps are colonoscopy, sigmoidoscopy, CT colonography (CT-C) and colon capsule endoscopy.

The data on the use of all of these screening methods will be discussed in the following part of the review: (i) methods that mainly detect cancers, i.e. faecal occult blood tests, genetic stool tests, septin-9 blood test, and M2-PK, and (ii) methods that detect cancers and polyps, i.e. colonoscopy, sigmoidoscopy, CT-C, and capsule endoscopy.

Faecal Occult Blood Tests

Faecal occult blood tests (FOBT) detect blood in the stool that is not visible to the eye. FOBT rely on the fact that colorectal neoplasms tend to bleed more often than normal mucosa. Two different test forms are available: guaiac-based (gFOBT) and immunochemical (iFOBT or FIT). Formerly, gFOBT used to be the most widely used test. It consists of two or three test fields that contain guaiac. If blood is present in the stool the haemoglobin (Hb) with its pseudoperoxidase activity will result in a blue colour change of the test field in the presence of hydrogen peroxide. Because colorectal neoplasms tend to bleed, intermittently testing several stool samples increases the yield. It has become standard to test three consecutive stools, i.e. to use three test slides for screening purposes. A test is positive if one or more of the six test fields turn blue. A positive test has to be followed up by complete colonoscopy.

Overall, five large randomized controlled trials, four from Europe and one from the USA, have shown that gFOBT is able to achieve a reduction in CRC-related mortality [1–6]. In a meta-analysis of four of these trials a reduction of CRC-related mortality of 16% for the whole

screening group was reported [7]. For those attending a least one round of screening, mortality reduction was 25%. All four European trials used a biannual screening design. In the US trial which included annual and biannual testing, CRC-related mortality was reduced by 21% in the biannual group and 33% in the annual group, suggesting an advantage for annual testing [1]. The mortality reduction by gFOBT is achieved by detecting asymptomatic cancers at an early stage with a better prognosis. However, because a one-time gFOBT has a moderate sensitivity of about 40%, a negative gFOBT has to be repeated regularly. The sensitivity of the gFOBT for adenomas is low (about 10–20%). Thus in all four European trials no reduction in cancer incidence was found. In the US trial a CRC incidence reduction of 20% after 18 years was reported [8], however the colonoscopy rate in this trial was 38% compared to 1.9–4.8% in the European trials. gFOBT are not specific for human blood and can be influenced by external factors.

Much attention has recently been paid to FIT. These tests only detect human blood in the stool and are considered more sensitive and specific than gFOBT. In a recent meta-analysis including 19 trials the pooled sensitivity and specificity for CRC of a one-time FIT was 79 and 94%, respectively, with an overall accuracy of 95% [9]. gFOBT and FIT have been compared in two large prospective randomized trials in the asymptomatic population from the Netherlands [10, 11]. In the first trial, 20,623 asymptomatic individuals between the ages 50 and 75 were randomized to undergo gFOBT (Hemoccult II) consisting of six test fields or FIT (OC-Sensor with a cut-off of 100 ng Hb/ml) consisting of a single stool sample [10]. Individuals were sent a test and an information brochure. Completed tests were mailed and centrally processed. People who did not respond received a reminder after 2 weeks. The participation rate in the FIT group was significantly higher than in the gFOBT group (59.6 vs. 46.9%). 5.5% of the returned tests in the FIT group and 2.4% in the gFOBT group were positive. 84% of participants with a positive test underwent colonoscopy, i.e. 16% did not undergo the recommended follow-up of a positive test. In the FIT group, 24 patients were diagnosed with a cancer compared to 11 patients in the gFOBT group. Furthermore, 121 patients in the FIT group compared to 48 patients in the gFOBT group were diagnosed with advanced adenoma (adenoma ≥ 1 cm, villous histology or high-grade dysplasia). Specificity of the FIT was 97.8% compared to 99% for the gFOBT. Overall in this trial the FIT was found to be superior to the gFOBT concerning the participation and detection rate of neoplasia. In a second trial from the

Table 1. Randomized trials on the efficacy of sigmoidoscopy screening

First author	Sigmoidoscopy group	Controls	Average age, years	Participation rate, %	Follow-up, years	Incidence of CRC (ITT)		Mortality from CRC (ITT)	
						distant colon	proximal colon	distant colon	proximal colon
Atkin [16]	57,237	113,195	60	71	11.2	0.64 (0.57–0.72)	0.98 (0.85–1.12)	0.69 (0.59–0.82)*	
Hoff [17]	13,823	41,913	59	64.8	7	not stated	not stated	0.63 (0.34–1.18)	not stated
Schoen [18]	77,445	77,455	not stated	83.5	11.9	0.71 (0.64–0.80)	0.86 (0.76–0.97)	0.50 (0.38–0.64)	0.97 (0.77–1.22)
Segnan [19]	17,148	17,144	not stated	58.3	11.4	0.76 (0.62–0.94)	0.91 (0.69–1.20)	0.72 (0.48–1.09)	0.79 (0.49–1.27)

* Only mortality data for all colon segments provided.

Netherlands with a similar design, 15,011 individuals were randomly assigned to undergo gFOBT (Hemoccult II), FIT (OC-Sensor with a cut-off of 100 ng Hb/ml) or sigmoidoscopy [11]. Again, the participation rate for the FIT group was significantly higher than in the gFOBT-group (61.5 vs. 49.5%). 4.8% of the returned tests in the FIT group and 2.8% in the gFOBT group were positive. Unlike the first study the proportion of individuals with a positive tests undergoing colonoscopy for work-up was higher (96%). In the FIT group, 14 patients were diagnosed with a cancer compared to 6 patients in the gFOBT group. Furthermore, 59 patients in the FIT compared to 22 patients in the gFOBT group were diagnosed with advanced adenoma (adenoma ≥ 1 cm, villous histology or high-grade dysplasia). The rate of advanced neoplasia (cancers and advanced adenomas) per 100 invited was significantly higher in the FIT than the gFOBT group (1.5 vs. 0.6%). Thus the results of this trial confirm the findings of the first trial showing a superior participation and detection rate of neoplasia for the FIT.

However, several questions remain. Although the detection rate of advanced adenomas is higher than for the gFOBT, it is currently unknown if this is sufficient to enable a measurable reduction in CRC incidence. In one study comparing different FIT available in Germany, sensitivity and specificity varied widely [12]. The results of one FIT therefore cannot automatically be transferred to another FIT with different test characteristics. The minimum test specificity that seems acceptable has to be defined according to the prerequisite of each country. The FIT used in the Dutch trials has the advantage that the test analysis can be performed automatically and the cut-off for a test to be considered positive can be adjusted without having to change the test. There is also an ongoing debate about the number of stool samples that should be tested. In the Dutch trial a one-sample test was used and this was superior to a three-sample gFOBT. In a Japanese

trial a two-sample FIT was found to be superior to a one-sample test. However, a recent analysis from a Dutch trial showed that adjusting the cut-off can result in a similar sensitivity as a two-sample test [13].

Endoscopic Methods

Endoscopic methods have the advantage of being able to detect cancers (including non-bleeding lesions) and confirming the diagnosis histologically. Furthermore, lower endoscopy has a high sensitivity for detecting and removing adenomatous lesions. The National Polyp Study using a case-control design reported more than 20 years ago that the removal of adenomas was associated with a CRC incidence reduction of up to 90% [14]. Recently, mortality data from this cohort were reported showing a reduction in CRC-associated mortality of 52% [15]. Two lower endoscopic methods are available: sigmoidoscopy and colonoscopy. Sigmoidoscopy is performed after application of an enema, usually without sedation, whereas colonoscopy requires complete bowel cleansing and is often performed using some form of sedation. However, colonoscopy enables the inspection of the whole colon whereas sigmoidoscopy only allows visualization of the sigmoid and rectum.

Sigmoidoscopy

There are four randomized studies examining the efficacy of sigmoidoscopy in CRC screening (table 1) [16–19]. Whereas the study from Norway was unable to show a significant decrease in CRC mortality [17] the other studies with a longer follow-up all showed a significant reduction in CRC mortality and incidence in the sigmoid colon and rectum. In the US study the protocol included

a second sigmoidoscopy 3 or 5 years after a normal examination [18]. Only the US study was able to show a modest reduction in proximal CRC incidence with no effect on proximal CRC mortality. The colonoscopy rate in this study was much higher than in the other trials (22 vs. 5%) which might be a possible explanation for the reduction in proximal CRC incidence reported in this trial. Overall these studies show that a one-time sigmoidoscopy can reduce CRC mortality and incidence of distal CRCs.

Colonoscopy

There are no data from randomized trials examining the effect of colonoscopy on CRC mortality and incidence. The results of three trials comparing colonoscopy to either no screening or FOBT will not be available for at least 10 years. However, there is indirect evidence in favour of a protective effect of colonoscopy. First, the reduction of FOBT on CRC mortality is due to colonoscopies being performed in case of a positive test. Second, case-control studies from the USA, Canada and Germany suggest a reduction of CRC mortality and incidence by colonoscopy [20–22]. Third, the reduction in incidence and mortality of distal CRC found in the sigmoidoscopy trials should be applicable to the whole colon for colonoscopy. An analysis of the association of CRC incidence and mortality with sigmoidoscopy and colonoscopy in two cohort studies comprising nearly 90,000 participants and a follow-up of 22 years was recently published [23]. In this trial both sigmoidoscopy and colonoscopy were associated with a reduced incidence and mortality of distal CRC, but only colonoscopy was associated with an effect on the cancers of the proximal colon. This study emphasizes the advantage of colonoscopy of being able to examine the whole colon. However in this analysis like in earlier studies the protective effect of colonoscopy was less pronounced in the proximal colon. The reasons for this likely include incomplete examinations, insufficient bowel preparation as well as missed lesions. A proportion of missed lesions probably consist of serrated neoplasias. The significance of serrated neoplasia which are mainly found in the proximal colon has evolved over the last few years. These lesions are easily missed as they are usually flat and often covered by a mucus cap. However, data from Germany suggest that the protective effect of colonoscopy in the right colon has recently improved [22]. Much effort has been put into decreasing the neoplasia miss rate by improvement of colonoscopy technique and imaging capability of endoscopes. In a recently published

prospective trial the adenoma miss rate of a new colonoscope with a 330° field of vision (full-spectrum colonoscopy) was compared to a standard colonoscope [24]. The miss rate of the full-spectrum colonoscopy was significantly lower compared to a standard colonoscopy (7 vs. 41%). The results are encouraging but have to be confirmed in additional studies. The miss rate in the standard colonoscopy group in this study seems unusually high.

In Germany, screening colonoscopy has been offered to anyone 55 years and older since 2002. An analysis of the data from the 2.8 million screening colonoscopies performed in the first 6 years show that a screening programme using highly qualified endoscopists can detect a significant number of adenomas and early-stage carcinomas [25]. However the experience in Germany also shows that the attendance rate of such a programme remains low and that more than 70% of participants have no neoplasia and would therefore not have needed a colonoscopy. Furthermore, the number of endoscopists required, costs and (although low) complication risk have to be considered.

CT Colonography

CTC is considered an attractive screening option by some experts. The examination consists of an abdominal CT scan that is usually performed after a complete bowel preparation and uses air or carbon dioxide distension of the colon. Using specially designed software the images obtained are reconstructed electronically and evaluated at a workstation by an observer for the presence or absence of structural colorectal lesions such as polyps and cancers. Patients found to have clinically important lesions are then referred for optical colonoscopy for biopsy or polyp removal. The results of large prospective studies using a screening population have been mixed [26]. In general a high detection rate (90% or higher) for polyps >9 mm has been achieved, the detection rate for polyps >5 mm was lower with 78–91% [27–29]. The referral rate to colonoscopy in the studies varied between 7.5 and 17.3% for a cut-off of 10 mm and 17.5 and 29.7% for a cut-off polyp size of >5 mm. It is currently unknown what the ideal cut-off for colonoscopy referral is.

There is emerging data suggesting that complete bowel preparation might not be required for CT-C [30–32]. Because stool has the same attenuation as the colon mucosa labelling the stool with a contrast agent is required (so-called faecal tagging). This is achieved by oral intake of barium or an iodinated contrast agent mostly starting 24–48 h before CT-C.

In a randomized trial from the Netherlands, eligible persons aged between 50 and 75 years were invited to a colonoscopy or a CT-C using a non-cathartic preparation with an oral iodinated contrast agent [33]. Patients with polyps >9 mm were referred to colonoscopy resulting in a colonoscopy rate of 9%. 8% of patients were offered surveillance CT-C after 3 years because of polyps 6–9 mm. The rate of advanced neoplasia in participants was significantly higher in the colonoscopy group (8.7 vs. 6.1%, $p = 0.02$). However, participation was higher in the CT-C group (34 vs. 22%, $p < 0.0001$). Thus the overall detection rate of advanced neoplasia per invitee was similar (colonoscopy group 1.9% vs. CT-C 2.1%). This study suggests a lower detection rate for CT-C but a higher participation rate which may result in a similar overall detection rate of advanced neoplasia.

CT-C is associated with radiation exposure. Modern CT scanners with a low-dosage protocol enable doses of <10 mSv. However, depending on the number of scans performed and the age of the screenings, an increased risk of malignancy does seem likely [34]. Other issues with CT-C include the unknown significance of extracolonic findings which required further work-up in 4.5 and 16% of the patients respectively [26].

MR Colonography

There is only limited data on the use of MR colonography (MR-C) for CRC screening. In a recent prospective study from Germany in 286 asymptomatic adults, sensitivities of 78.4 and 75% for adenomas >5 mm and advanced adenomas were reported with a specificity of 95.3% [35]. More data are needed before any recommendations concerning the use of MR-C for CRC screening can be made. Compared to CT-C, MR-C is not associated with radiation exposure. However the availability of MR scanners is much more limited and currently water is used for distension which can be unpleasant for the patient.

Capsule Endoscopy

Capsule endoscopy has been found to be a valuable diagnostic tool in the examination of the small bowel. There is less data of the use of capsule endoscopy for the colon. In the largest prospective study examining colon capsule endoscopy in a cohort of 328 patients with known or suspected colon disease using colonoscopy as the gold standard, the sensitivity for cancers was 74 and 73% for

advanced adenomas with a specificity of 79% [36]. In a meta-analysis examining data from eight studies with 837 patients, a sensitivity of 76% for cancers and 71% for polyps with a specificity of 75% was reported [37]. Results using a second-generation colon capsule version showed a higher sensitivity of 84% for polyps >5 mm with a specificity of 64%. If only polyps >9 mm were included the sensitivity was 88% with an increased specificity of 95% [38]. These studies included a mixed group of patients and currently there is no larger study with a screening population. Furthermore, it has to be kept in mind that the bowel preparation required for colon capsule endoscopy is even more rigorous than for colonoscopy.

Genetic Stool Testing

Genetic stool tests detect mutations in stool that can be found in CRC and to a lesser extent in adenomas. A large prospective trial from the USA compared a stool test consisting of a faecal DNA panel of 21 genetic changes and a gFOBT [39]. The genetic test was found to be superior to gFOBT for the detection of cancers with a sensitivity of 51.6 vs. 12.9%. The sensitivity for advanced adenomas was low for both tests (15.1 vs. 10.7%). Overall the results of this trial were disappointing. A later analysis of the test results concluded that the disappointing performance of the faecal DNA panel was at least partly caused by an inadequate stability of the stool DNA as well as imperfect extraction of the DNA. A test with a modified DNA stabilization and extraction method was able to increase the sensitivity of the test to 72.5% in a patient group with known cancers [40]. More recently, methylated genes have been shown to be associated with CRC. In a large prospective trial published this year, a genetic stool test consisting of KRAS mutation analysis, two methylation markers and Hb measurement was compared to a FIT. The sensitivity of the genetic stool test was significantly higher for the detection of cancers (92.3 vs. 73.8%) and advanced adenomas (42.4 vs 23.8%). However, specificity was significantly lower with 86.6 versus 94.9% [41]. Thus, genetic stool testing might be an interesting screening method for the future.

M2-Pyruvate Kinase

M2 is an isomer of the enzyme pyruvate kinase (M2-PK) that has an important role in glycolysis. M2-PK can be isolated in stool. Most studies looking at a possible role

Table 2. Screening recommendations in different guidelines

Guidelines	Publication year	Summary of recommendations
European guidelines [47]	2010	Good evidence that gFOBT reduces CRC mortality Reasonable evidence that FIT reduces CRC mortality Reasonable evidence that sigmoidoscopy reduces CRC mortality and evidence Limited evidence on efficacy of colonoscopy screening in reducing CRC mortality and incidence CT-C, stool DNA testing and capsule endoscopy should not be used for screening of average-risk population
Guidelines by the American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, American College of Radiology [45]	2008	Tests that detect adenomatous polyps and cancer: sigmoidoscopy every 5 years, or colonoscopy every 10 years, or double contrast barium enema every 5 years, or CT-C every 5 years Tests that primarily detect cancer: annual gFOBT with high test sensitivity for cancer, or annual FIT with high test sensitivity for cancer, or stool DNA, with high sensitivity for cancer, interval uncertain
Asia-Pacific guidelines [46]	2008	FOBT (guaiac-based and immunochemical tests), flexible sigmoidoscopy and colonoscopy are recommended for CRC screening Double-contrast barium enema and CT-C are not preferred
German guidelines [48]	2013	Colonoscopy every 10 years is the preferred test Alternative tests: sigmoidoscopy every 5 years or annual FOBT (guaiac-based); FIT with specificity of at least 90% can be used alternatively to gFOBT

for CRC screening have been performed in patients with known cancers or an increased risk for CRC. These studies suggest a sensitivity of about 80% for the detection of CRC [42]. The sensitivity for advanced adenomas is lower with 22% reported in one prospective study [43]. Specificity was reported as 82% in one study and thus might be an issue. Due to the lack of a large study in the asymptomatic population the exact efficacy of this test for CRC is currently unknown.

Blood Tests

Blood tests would be an attractive screening method as this would only require a sample of blood that can usually be easily obtained. Data of a large prospective screening study from Germany and the USA with the methylation marker septin-9 using colonoscopy as reference method were recently published [44]. In this study, 53 cancers and 315 adenomas were detected. The sensitivity for cancers using duplicate PCR replicates was moderate (48.2%) and low for advanced adenomas (11.2%). Specificity was acceptable with 91.5%. Due to the low sensitivity for advanced adenomas, this test does not seem suitable for primary cancer prevention. Con-

sidering the much higher costs of this test compared to FOBT or FIT, the possible role of blood tests in CRC screening remains to be defined and more studies are needed.

Summary of Guidelines

Table 2 lists a selection of available screening guidelines. The US multi-society taskforce guidelines recommend a wide selection of tests for screening including genetic stool testing and contrast barium enema [45]. The Asia-Pacific guidelines favour FOBT, FIT, sigmoidoscopy and colonoscopy [46]. The more recent European guidelines state that there is evidence in favour of FOBT, FIT, sigmoidoscopy and colonoscopy and in one chapter conclude that FIT is the screening test of choice [47]. On the other hand, screening with CT-C, genetic stool testing and capsule endoscopy are discouraged. In the most recent German guidelines, colonoscopy is recommended as the preferred screening test. In patients unwilling to undergo colonoscopy sigmoidoscopy or FOBT should be used alternatively. FIT with a specificity of more than 90% can be used instead of FOBT [48].

Conclusion

There is strong evidence in favour of CRC screening that should be performed in form of an organized programme with regular outcome monitoring. A variety of screening tests are available. The characteristics of each of these tests are given in this review. Depending on available resources, each country will have to make a choice on the screening method to be used. If the main aim of screening is the early detection of cancers there is good

evidence for the use of FIT. If the aim includes the detection of adenomas, endoscopic methods are likely more appropriate. The role of CT-C, capsule endoscopy, genetic stool tests, blood tests and M2-PK is currently unknown.

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