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REVIEW

Strategies in screening for colon carcinoma

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ABSTRACT

Colorectal cancer is the second most common cancer in Europe and meets the criteria for population screening. Population screening should lead to a reduction in CRC-related mortality and incidence. Several options are available for CRC screening, which can be itemised as stool-based tests and structural exams. Stool-based tests include guaiac and immunochemical faecal occult blood tests and DNA-marker tests. Structural exams comprise endoscopic techniques (flexible sigmoidoscopy, colonoscopy and capsule endoscopy) and radiological exams (double contrast barium enema, CT colonography and MR colonography).

Each test has its own test performance characteristics and acceptability profile, which affect the participation and effectiveness of the associated screening programmes. Faecal occult blood tests (FOBT) and flexible sigmoidoscopy (FS) are the only methods with a demonstrated mortality reduction during a ten-year period (FOBT 16% and FS 31%) while flexible sigmoidoscopy is the only screening test with a demonstrated reduction in CRC incidence (23%). It is likely that other screening techniques such as colonoscopy and CT colonography will also be effective in the reduction of CRC-related mortality. DNA-marker tests, capsule endoscopy and MR colonography are possible options for the future.

Keywords: Colorectal cancer, mass screening, screening test

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in Europe. Each year, more than 400,000 persons are diagnosed with CRC and more than half of them will die from the disease.[1] In the Netherlands, 12,117 persons were diagnosed with CRC and 4810 persons died from CRC in 2008.[2,3] The clinical and pathological stage at the time of diagnosis largely determines the prognosis of diagnosed patients.[4] The CRC mortality rate could be decreased by the early detection of cancer, whereas both the mortality rate and the incidence can be decreased by the timely detection and removal of adenomatous polyps, precursor lesions of CRC.[5] As clinical symptoms develop late in the course of the disease, early detection requires additional action.

One of the ways of achieving early detection and prevention is through the development of population screening programmes in asymptomatic individuals.[6-9] CRC screening meets the criteria for population screening as defined by Wilson and Jungner.[10] CRC is an important health problem; its precursor lesions are recognisable and early removal of these lesions has been shown to be beneficial.

Several CRC screening tests are available. Each test has its specific test characteristics, with particular advantages and disadvantages that determine its acceptability profile.

In general, screening tests can be classified into two categories: stool-based tests and structural exams. Stool-based tests can be subdivided into tests that detect blood (guaiac and immunochemical faecal occult blood tests) and tests that detect faecal DNA that is shed from CRC. Structural exams can be subdivided into endoscopic techniques (flexible sigmoidoscopy, colonoscopy and capsule endoscopy) and radiological exams (double contrast barium enema, computed tomography (CT) colonography and magnetic resonance (MR) colonography). In this review, we discuss test performance, participation rate and effectiveness of the available population screening tests for CRC.

SCREENING TESTS

Stool-based tests

Faecal occult blood tests (FOBT) are based on the principle of detecting blood in stool that may originate from a bleeding CRC or large adenoma. FOBT is frequently used as

screening test worldwide because it is simple to perform at home, is non-invasive and relatively cheap. However FOBTs are not designed to detect precursor lesions. Adenomas and even CRCs usually bleed intermittently and therefore repetitive testing is required. Two main classes of FOBTs are available: guiac-FOBT (gFOBT) and faecal immunochemical tests (iFOBT or FIT). gFOBT detect any blood in stool whereas FIT are more specific for human haemoglobin.

Guiac-faecal occult blood test (gFOBT)

gFOBT detects blood in stool through pseudoperoxidase activity of haeme or haemoglobin. Persons are invited to collect three samples of stool at home and send it back by mail. The result of the test is usually interpreted by a laboratory assistant. In case of a positive test result, follow-up colonoscopy is advised. The test itself is easy to perform at home and no serious complications can be expected. In contrast, follow-up colonoscopy can cause complications in FOBT-based screening programmes, such as perforation and bleeding (0.001 to 0.02%).[11]

Test performance

Sensitivity is affected by factors such as test interpretation variability among laboratory assistants, brand of the test, and number of stool samples collected. Sensitivity is increased by adding a drop of water to the test before processing (rehydration of the test). Dietary intake of red meat (detection of non-human haemoglobin) leads to false-positives and vitamin C intake to false-negatives through blockage of the peroxidise reaction. gFOBT sensitivity is limited and variable for CRC (reported numbers vary between 13 and 64%) and for advanced adenomas (11 to 41%). Specificity for CRC ranges from 91 to 95%.[11-13] In population screening, the non-rehydrated gFOBT resulted in a low test positivity rate (0.8 to 3.8%) and a positive predicted value (PPV) for CRC of 5.0 to 18.7%. Rehydrated gFOBT resulted in a higher test positivity rate (1.7 to 15.4 %) and a lower PPV (0.9 to 6.1%) than non-rehydrated gFOBT.[11]

Participation

To be effective, gFOBT-based screening programmes require annual or biannual testing. Therefore, participation in subsequent screening rounds is essential. Reported percentages of persons attending a first gFOBT screening round ranged from 53 to 67%. The percentages of persons attending all screening rounds were only between 38 to 60% while participation in at least one of the screening rounds was between 60 to 78%, in a programme with a minimal length of ten years.[11,14]

Effectiveness

gFOBT was the first screening test with a documented CRC-related mortality reduction during a ten-year period.[11,14] The estimated CRC-related mortality reduction ranged from 13 to 33% in four randomised controlled trials (RCTs), in which FOBT screening was compared with no screening. Combining the results of all eligible RCTs that used both annual and biannual screening leads to an estimated 16% RR reduction in CRC mortality in an intention-to-screen meta-analysis (RR 0.84; 95% confidence interval [CI] 0.78 to 0.90). In studies that only used biannual screening an estimated 15% CRC mortality reduction (RR 0.85; 95% CI 0.78 to 0.92) was achieved, from which can be concluded that biannual screening is sufficient.[11] A CRC incidence reduction was only observed in one RCT, but this effect could be largely attributed to the high colonoscopy and following polypectomy rate in that study. The other three (truly population-based) RCTs reported no significant CRC incidence reduction.

Immunochemical faecal occult blood test (FIT)

FIT detects human globin in stool via an immunochemical reaction and is generally considered a superior screening test compared with gFOBT. Whereas gFOBT only determines the presence or absence of blood in stool in absolute terms, FIT allows quantitative measurement of haemoglobin in stool. This allows fine-tuning of the cut-off level for referral for follow-up colonoscopy, aiming at an optimal balance between test performance and the available colonoscopy capacity in a certain country.[15,16] In contrast to gFOBT testing, no dietary restrictions are needed. Processing of the test is automated in a clinical laboratory and only one measurement is needed for FIT, versus three stool samples for gFOBT-based screening. As adverse events are also associated with follow-up colonoscopies rather than with stool testing itself, complication rates of FIT-based screening programmes will be comparable with that of gFOBT-based screening, provided the positivity rates are comparable.

Test performance

With FIT, high sensitivity can be achieved. Its sensitivity in detecting CRC (66 to 82%) and advanced adenomas (27 to 30%) is at least similar to that of gFOBT, without a reduction in CRC specificity (95 to 97%).[12,17] In persons who participated in screening, detection rates for advanced adenomas and cancer were higher with FIT compared with gFOBT (2.4% *vs* 1.1 to 1.2%) whereas the PPV for CRC seems equal (10 to 11% *vs* 8.6 to 9.7%).[18,19]

Participation

In two Dutch population-based screening studies, in which participants were randomised to receive either gFOBT or FIT, participation was higher in the FIT group (60 and 62%) than in the gFOBT group (47 and 50%).[18,19] However, participation in the gFOBT-screening arm in these trials was lower than in other European studies (53 to 67%). This

could be due to the current low awareness of CRC and CRC screening in the Netherlands.[20,21] However this could also imply an increase in participation for FIT-based screening in the future. The most important reason for the higher participation rates for FIT screening is presumably the easier performance of the test.[22]

Effectiveness

There is no evidence from RCTs that CRC-related mortality is reduced over a ten-year period of FIT screening. Because FIT-based screening has been shown to lead to higher participation and detection rates than gFOBT-based screening, it is likely that the associated effectiveness is at least comparable. In one RCT 94,000 persons were randomised to either one round of FIT testing and completion of a risk questionnaire or no screening.[23] No colon cancer mortality reduction was shown after a follow-up period of eight years: CRC mortality was 90 per 100,000 in the screening group *vs* 83 per 100,000 in the control group (p=0.222). There were some major limitations is this study: only one round of FIT was offered and flexible sigmoidoscopy instead of colonoscopy was performed in case of a positive test result.

DNA markers

A relative new method of CRC screening is based on DNA markers in stool (sDNA) and carries promise for screening in the future. A multipanel of DNA markers is needed because no single gene mutation is present in all cells shed by adenoma or cancer. A panel of DNA markers comprising selected point mutations on APC, KRAS and p53 genes plus long DNA (PreGen-Plus) is being tested in two large average-risk cohorts.[13] Another panel marker comprising methylated vimentin, mutant KRAS, and mutant APC (SDT-2) is being tested in a smaller study.[24] However, costs are high compared with FOBT.

Test performance

One study that used PreGen-Plus showed a limited CRC sensitivity (52%) and acceptable specificity (94%).[13] Another study using PreGen-Plus showed 20% sensitivity and 96% specificity for 'screen-relevant neoplasia' (curable-stage cancer, high-grade dysplasia, or adenomas > 1 cm). This study also reported a sensitivity of 40% for screen-relevant neoplasia using SDT-2.[24] The limited sensitivity can be explained by the use of a panel of DNA markers identifying the majority but not all CRC.

Participation

So far, no studies have been performed evaluating sDNA in an invitational population-based screening setting. It is not known to what extent individuals would be more willing to participate in CRC screening by sDNA than by gFOBT or FIT.

Effectiveness

No data are available evaluating reduction of CRC-related mortality by sDNA during a period of ten years.

ENDOSCOPIC TECHNIQUES

Flexible sigmoidoscopy

Flexible sigmoidoscopy (FS) is an endoscopic procedure, in which the distal 40 to 60 cm of the colon is inspected by a regular forward viewing endoscope. Individuals will receive an enema 30 to 60 minutes before the examination for distal bowel cleansing. FS can be performed without sedation. In contrast to FOBT testing, small early neoplastic lesions in the distal colon are detected and these can directly be removed. If an adenoma of any size is detected in the distal colon a full colonoscopy is advised, because of the increased risk of advanced adenomas or cancer in the proximal colon.[25] Quality of the examination and thus of the screening programme might be difficult to assess since insertion depth is sometimes difficult to determine.[26] Furthermore, FS needs to be performed by trained endoscopists with acceptable adenoma detection rates.[26] Complications such as bleeding or perforation occur in FS screening, because of the screening method itself (0 to 0.03%) or due to follow-up colonoscopy (0.3 to 0.5%).[27-29]

Test performance

In a screening programme in which eligible patients were selected by general practitioners (GP), FS had a higher detection rate for advanced adenomas and cancer compared with FIT in one screening round (5.2 *vs* 1.2%, OR 0.22; 95% CI: 0.14 to 0.35%).[30] Isolated proximal advanced adenomas or cancer will be undetected in persons attending FS screening, because, in the absence of distal adenomas, they will not receive a follow-up colonoscopy. In persons attending colonoscopy screening, the percentage of asymptomatic individuals with isolated proximal advanced adenomas or cancer is estimated at 1.3 to 5%.[31,32]

Participation

Participation to once-only FS screening is lower than in once-only gFOBT or FIT screening.[19] However the large variance of participation rates to FS screening is remarkable in Europe. A Dutch trial reported a participation rate of 32% whereas large Norwegian and UK trials have reported participation rates of 64 and 71%.[19,27,28] The Norwegian and Dutch trials were truly invitational population-based whereas the UK trial used a two-step procedure in which people were only randomised after having shown an interest in being screened. Screening

programme participation could be lower over ten years because it is generally advised that repetitive five yearly testing is necessary in case of a negative test result.[33]

Effectiveness

Recently, Atkin *et al*. (UK trial) were the first to show evidence of mortality reduction in FS screening.[27] In contrast to FOBT screening, a CRC incidence reduction was also expected because of the removal of the precursor lesions in FS screening. After having shown an interest to be screened, asymptomatic individuals were randomised on a 2:1 basis resulting in a control group (113,195 persons) and an intervention group (57,237 persons). In the intervention group, 40,621 persons (71%) attended FS screening; advanced adenomas or cancer was detected in 5%. In all people offered a single round of FS screening, a 23% reduction of CRC incidence (HR 0.77; 95% CI 0.70 to 0.84) and a 31% reduction in CRC related mortality (HR 0.69; 95% CI 0.59 to 0.82) were observed. In persons who actually attended FS screening, the incidence and mortality reduction were higher: 33% (HR 0.67; 95% CI 0.60 to 0.76) and 43% (HR 0.57; 95% CI 0.45 to 0.72), respectively. A Norwegian group reported the results of an interim analysis of a population-based study (NORCCAP trial) for CRC incidence after a follow-up period of seven years and for CRC mortality after six years.[28] In contrast to the UK trial, no significant difference was found in CRC incidence between the screening and control group (134.5 *vs* 131.9 cases per 100,000 person-years). Nor was a significant difference observed in CRC-related mortality (HR 0.73; 95% CI 0.47 to 1.13). There was a significant CRC-related mortality reduction of 59% in persons who actually attended FS screening (HR 0.41; 95% CI 0.21 to 0.82). Hoff *et al*. mentioned two reasons for the limited effect of FS screening in this interim analysis: the screening test does not work or the development of CRC from precursor lesions will take longer than the follow-up time. The second possibility is more likely, considering the results of the UK trial.

Two other large RCTs of FS screening are currently ongoing. The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial included 154,942 men and women aged 55 to 74 years, who were randomised to either repeated FS or no screening.[34] In the Italian SCORE trial, 34,292 individuals were randomised to either once-only FS-based screening or no screening.[29]

Colonoscopy

Colonoscopy is an endoscopic technique that allows inspection of the entire colon. It is considered the reference standard for detection of colorectal neoplasia. Colonoscopy is an invasive and burdensome procedure and involves full bowel cleansing. The main advantage of colonoscopy is that removal of adenomas or early cancer can be performed during the same procedure whereas all other screening tests require colonoscopy for confirmation and removal. Another advantage is that histological assessment of resected polyps and irresectable lesions can be directly obtained, which is necessary to determine the surveillance interval or the need for further treatment. The risk of complications with colonoscopy is estimated between 0.1 and 0.3%; adverse events include postpolypectomy bleeding and perforation.[35,36]

Test performance

In an average risk cohort of persons 50 to 66 years of age who underwent full colonoscopy, advanced adenomas were detected in 5% and CRC in 0.9%.[36] Although colonoscopy is considered to be the reference standard for the detection of colonic neoplasia, polyps are still missed. A substantial adenoma miss rate of 20 to 26% for any adenoma and of 2.1% for large adenomas (≥10 mm) was reported in tandem colonoscopy studies.[37] Adenoma detection rate is highly dependent on quality standards including the colonoscopist and several patient-related factors.[38] Optimal bowel preparation, sufficient withdrawal time, complete examination of the colon and, to a lesser extent, optimal withdrawal technique, are associated with lower polyp miss rates.[39-42]

Participation

It is not known yet to what extent persons would participate in a truly invitational population-based colonoscopy screening programme. Colonoscopy is offered in Poland and Germany as part of an implemented programme.[36,43] In Germany, the average annual participation rate is about 2.6% of those entitled to screening colonoscopy: men and women aged 55 years or older.[44] The Italian study reported a lower participation rate for colonoscopy screening compared with FS and FIT screening: 27% *vs* 32 and 32%, respectively.[30] In this study, subjects were selected by GPs and randomised to one of the groups within GP. This study can not therefore be considered an invitational population-based screening study.

It would come as no surprise that participation rates in colonoscopy screening are lower than in FOBT or FS-based screening, because the procedure is simply more invasive and burdensome. Yet, as patients only have to participate once every ten years, achieving comparable programme adherence over a similarly long period could be challenging for FOBT and FS-based screening. Colonoscopy can be performed with long intervals as the risk of developing CRC after a negative colonoscopy remains low for more than ten years.[45,46]

At this moment, a large Spanish RCT is ongoing comparing the participation rate in biannual FIT screening to that of one-time colonoscopy screening, with a follow-up time of ten years.[47] A Dutch RCT (COCOS trial) is ongoing,

comparing participation in one-time colonoscopy screening to that in one-time CT-colonography screening.[48] This trial is conducted in the same setting as earlier RCTs in the Netherlands which investigated participation rates in gFOBT, FIT and FS based screening, allowing a comparison, be it an indirect one, of all of these screening tests.

Effectiveness

There are no empirical estimates of the effects of colonoscopy screening on CRC-related incidence and mortality. The Nordic-European Initiative on Colorectal Cancer (NordICC) trial is a multicentre collaborative effort in the Nordic countries, the Netherlands and Poland in which 66,000 individuals are randomised to either colonoscopy screening or no screening. A 15-year follow-up is planned and an interim analysis will be performed after ten years. Results are expected in 2026.[49] In the Spanish trial, CRC-related mortality is directly compared between biannual FIT and colonoscopy screening and results are expected in 2021.[47]

Capsule endoscopy

Colon capsule endoscopy is a new technique to visualise the colon, originating from small bowel imaging. Colon capsule is an ingestible capsule consisting of an endoscope equipped with a video camera at both ends. Van Gossum *et al*. were the first to evaluate the effectiveness in a prospective setting. In high-risk patients, the sensitivity and specificity in detecting polyps ≥6 mm was 64 and 84% respectively and in detecting advanced adenomas 73 and 79%.[50] The per-patient sensitivity and specificity with the second-generation capsules were promising, with an estimated sensitivity and specificity of 89 and 76% for polyps ≥6 mm, and 88 and 89% for polyps ≥10 mm.[51] Compared with full colonoscopy, the accuracy of capsules is considerably lower and an even more extensive bowel cleansing is needed. Capsule endoscopy has not yet been evaluated in an average risk screening population.

RADIOLOGICAL EXAMS

CT colonography

CT colonography (CTC), also called virtual colonoscopy, allows an examination of the entire colon. Interpretation is made possible in two-dimensional and three-dimensional images. A small rectal catheter is inserted into the coecum and carbon dioxide is needed for bowel insufflation. CTC is considered a less invasive colonic exam compared with colonoscopy.[52,53] The preparation is reduced to 150 ml of iodinated contrast agent for tagging combined with a low residue diet. This preparation is now indicated as best practice and can replace the extensive bowel preparation needed for colonoscopy.[54] If polyps or CRC are detected on CTC, a colonoscopy will follow for confirmation and, if possible, subsequent therapy. CTC screening leads to exposure of ionising radiation to asymptomatic persons. A low-dose protocol is regularly used and inherent chances of radiation-induced malignancy are low. Extra colonic structures are made visible on CTC. This could be beneficial, but the risks and costs associated with false-positives will be considerable. The risk of complications is extremely low, no perforations or other serious complications have been observed in a large CTC screening cohort.[55]

Test performance

A large screening trial evaluating CTC and same day colonoscopy studied 1233 asymptomatic individuals and reported high sensitivity (94%) and specificity (96%) per patient for large adenomas (≥10 mm) and these dropped for smaller lesions (≥6 mm): 89 and 80% respectively.[56] In another study, performed across 15 institutions and including 2500 asymptomatic individuals, sensitivity for adenomas ≥10 mm and cancer was 90%, specificity 86%, at a PPV of 23% and an NPV of 99%.[57] The diagnostic yield for detection of advanced neoplasia of CTC is comparable with that of colonoscopy: 3.2 *vs* 3.4%.[55]

Participation

So far, no data are available evaluating participation to an invitational population-based CTC screening programme. The ongoing Dutch COCOS trial compares participation in CTC-based screening to that in colonoscopy screening.

Effectiveness

The effectiveness of CTC screening on CRC incidence and mortality has not yet been demonstrated. To our knowledge, no RCTs are ongoing evaluating this effect.

MR colonography

Magnetic resonance imaging (MRI) of the colon has been increasingly studied in the last years. This imaging technique also allows examination of the entire colon. The lack of ionising radiation and high soft tissue contrast could favour MRI over CTC. As in CTC, the use of ionising contrast agent for tagging could be mandatory.[58]

Accuracy of MR colonography in detecting colorectal polyps was evaluated in both high-risk and normal-risk cohorts. In a meta-analysis, its sensitivity in the detection of CRC was estimated at 100%. For polyps with a size ≥10 mm, per-patient sensitivity and specificity estimates were 88 and 99%.[59] One study only included asymptomatic individuals with a normal risk for CRC. Sensitivity and specificity for polyps ≥10 mm were 70 and 100%.[60]

Double-contrast barium enema

Double contrast barium enema (DCBE) was the first radiological exam that could evaluate the entire colon. DCBE coats the mucosal surface with high-density barium. Multiple radiographs are made while constantly changing the patient's position. Full bowel preparation is needed and test performance is low: sensitivity for lesions ≥10 mm and ≥6 mm is only 48% and 35% respectively in a high-risk cohort.[61] The higher performances of CTC and MR colonography make DCBE-based screening studies illogical.

DISCUSSION

Of all available options for CRC screening, gFOBT and FS-based screening are the only strategies with a documented CRC-related mortality reduction during a ten-year period. gFOBT and FS-based screening can therefore considered to be effective.[11,27] Development in CRC screening is ongoing and it is very likely that other screening methods (iFOBT, CTC and colonoscopy) are effective as well. Stool marker tests, capsule endoscopy and MR colonography should not be used for CRC screening at this moment, but have potential for the future. DCBE is considered to be an inferior modality, now surpassed by CTC, and should not be used for screening. The characteristics of all screening tests are summarised in *table 1*.

FOBT is easy to perform at home and the associated costs are low. FOBT requires biannual testing and follow-up colonoscopy is needed in case of a positive test result. High participation rates during both first and subsequent screening rounds are essential for the effectiveness of the screening programme. Nowadays FIT-based screening is generally preferred over gFOBT-based screening, because of the better participation and detection rates. Its quantitative nature allows the definition of an optimal cut-off level aiming to match detection rates in a given population to colonoscopy capacity. However, definitive evidence of the effectiveness for FIT-based screening is lacking.

In contrast to FOBT, CRC-related incidence reduction was observed in FS-based screening. It is very likely that colonoscopy-based screening would also result in CRC-related incidence reduction. The success of FS-based and colonoscopy-based screening is dependent on the quality of the examination which should be carefully guaranteed if implemented. Colonoscopy is considered the best test to detect colorectal neoplasia, but polyps are missed by this modality as well. CTC can detect polyps with similar accuracy compared with colonoscopy and is therefore also a good candidate for CRC screening.

To implement a specific CRC screening programme, various factors should be taken into account. Besides factors as test accuracy and participation rates, programme adherence has already been proven necessary (biannual screening by FOBT). However high test accuracy is often associated with high burden and low programme adherence. Furthermore, high participation rates of a single round of screening would not automatically result in high programme adherence during a longer period. The results of the interim analysis of the NORCCAP study may illustrate that programme adherence for FS screening is as important as for FOBT screening. No significant CRC-related mortality reduction was shown after seven years of follow-up by a single round of (invitational population-based) screening. This might indicate that a second round after five years is actually needed.[28] It seems logical that a CRC-related mortality reduction will be shown in the future, because development to CRC will probably take longer than seven years. This is confirmed

Table 1. *Characteristics of all screening tests*

	gFOBT	FIT	FS	CTC	Colonoscopy
Sensitivity (%) for detecting cancer or advanced adenoma[62]	20	32	83	97	100
Detection rate for advanced adenoma and cancer (%) intention-to-treat[18,19,30,36,55]	1.1[19] to 1.2[18]	1.2[30] to 2.4[18,19]	5.2[30] to 8.0[19]	3.2[55]	3.4[55] to 5.9[36]
Participation rates (%) in the Netherlands[18,19,48]	47[18] to 50[19]	60[18] to 62[19]	32[19]	expected in 2011[48]	expected in 2011[48]
Complication rate (%) in population screening screening test only + colonoscopy	- 0.001-0.02	- 0.001-0.02	 0-0.03 0.3-0.5	expected in 2011[48] expected in 2011[48]	0.1-0.3 N/A
Significant reduction CRC incidence (%) intention-to-screen[11,27]	No[11]	No	23[27]	?	?
Significant reduction CRC mortality (%) intention-to-screen[11,27]	16[11]	?	31[27]	?	?

[62]colonoscopy is used as reference standard; [18,19]derived from population-based RCT; [30,36,55]derived from non-population invitational based screening programme; [11]CRC incidence reduction was not found by three of four RCTs included in meta-analysis

by the results of the UK trial, but this study used a two-step invitation strategy and can not be considered to be truly invitational population-based.[27]

In the US, persons can choose the screening test that they prefer. Two major US guidelines, from ACS-MSTF and USPSTF, both published in 2008, came to different recommendations on CRC screening while the literature supporting both guidelines was almost identical.[33,63] ACS-MSTF distinguishes between cancer *prevention* tests and cancer *detection* tests. The cancer prevention tests are mainly focussed on detection and removal of the premalignant lesions to prevent development of cancer while the cancer detection tests concentrate mainly on early detection of cancer. ACS-MSTF stipulated that the best test is the test that the patient will take, but recommends cancer prevention over cancer detection tests. In contrast, the USPSTF guidelines are based on a simulation decision model and require a higher level of evidence to include a test. The USPSTF recommend focusing on strategies that maximise the participation rate and therefore also includes cancer detection tests in their guidelines.

In most of the EU member states, the USPSTF approach is more supported than the ACS-MSTF one. The Council of the European Union (EU) has recently recommended screening by FOBT, but a population-based approach to programme implementation. Most of the EU member states have already adopted this approach.[64] Some of the member states (Germany, Austria) have established non-population-based screening programmes while some have implemented other strategies than FOBT. Poland began an opportunistic colonoscopy programme in the early 1990s and also other member states have adopted endoscopic methods (Austria, Germany, Greece), as a supplement to FOBT or an alternative screening method. Differences in programmes and strategies might make it difficult to evaluate and to compare the effect of screening in all of Europe.

In conclusion, strong evidence is available on the effectiveness of FOBT screening.[11] FOBT, and especially FIT, resulted in the highest participation rate in pilot programmes.[18,19] Most of the EU member states have now implemented or will implement a FOBT programme. However, other screening techniques (FS, colonoscopy, CTC, MR colonography or stool marker tests) could be implemented as a supplement in existing programmes or replace FOBT in the future.

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