Population-based screening for colorectal cancer

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On ne voit bien qu'avec le cœur. L'essentiel est invisible pour les yeux.
Alleen met het hart kun je goed zien. Het wezenlijke is voor de ogen onzichtbaar.

Antoine de Saint-Exupéry, Le Petit Prince.

Voor mijn ouders

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Chapter 1

Introduction and outline of the thesis

EPIDEMIOLOGY OF COLORECTAL CANCER

The incidence of colorectal cancer (CRC) shows considerable geographical differences around the world. The highest incidence rates are mainly seen in the Western world including North America, Australia/New Zealand, Western Europe, and Japan. Development countries report the lowest incidence rates. In Europe, CRC is the second most common diagnosed cancer in women and third in men (13% of all cancer cases in both women and men). Incidence rates are somewhat higher in men (1.2:1.0). The lifetime incidence of CRC in patients at average risk is approximately five percent.[1] Incidence rates show demographic disparities over the last decades, with a gradual increase in South/Eastern Europe, stabilising numbers in North and West Europe, and a declining trend in the United States.[2-4] Age is a major risk factor for the development of CRC. CRC rarely develops before the age of 40 (IKC), except in patients with a genetic predisposition.[5, 6] Incidence rates rapidly increase beyond the age of 50.[2, 3]

In Europe, CRC ranked second (12% of all cancer related mortality) in terms of cancer related mortality [1], despite the significant increase in five-year survival in the last two decades.[7] This improvement was in particular due to resection of rectal cancer with sharp dissection of the mesorectum en bloc with the rectum (total mesorectal excision) combined with pre-operative radiotherapy [8], and usage of new chemotherapeutic agents in various combinations.[9] Additionally, improvement in outcome can be attributed to detection of the disease at an earlier stage due to screening and surveillance programmes.

RISK AND PREVENTIVE FACTORS OF COLORECTAL CANCER

Several environmental factors are associated with the development of CRC. Alcohol consumption of more than 45g/day (relative risk (RR) 1.4; CI 1.2 to 1.7), cigarette smoking (RR 1.2; CI 1.1-1.3), and consumption of more than 120g/day of red or processed meat (RR 1.3; CI 1.2-1.4) are significantly associated with an increase in CRC incidence.[10-12] Furthermore, obesity has been identified as risk factor for CRC incidence and mortality.[13-16] Individuals with a body mass index (BMI) of over 40 are significantly more likely to die from CRC (RR 1.5-1.6). A meta-analysis estimated a 30% increase in risk on CRC among diabetics compared to non-diabetics (RR 1.3 CI 1.2-1.4).[17]

Recently, aspirin use has been identified as primary prevention of CRC most likely by inhibiting the malignant transformation of adenomas.[18, 19] At least 300 mg aspirin a day for about five years reduced the incidence of CRC with 10-year latency (Hazard ratio 0.74). No association between calcium + vitamin D supplementation or folic acid usage and CRC incidence has been established so far.[20-22] Regular physical activity, either occupational or leisure time, does have a preventive effect on the development of CRC (RR 0.76, CI 0.72-0.81).[23]

RISK STRATIFICATION

Nation-wide screening programme are designed for average risk individuals.[24] Individuals with a history of adenomas [25], previous CRC, inflammatory bowel disease; a first degree relative with CRC diagnosed ≤ 60 years [26, 27]; or a hereditary cancer syndrome [5, 6] are at increased risk for CRC and should enter specialised screening or surveillance programmes.[28]

SCREENING FOR COLORECTAL CANCER

CRC fulfils the screening and surveillance criteria of Wilson and Jungner [29], i.e. the disease poses an important health problem with significant morbidity and mortality, the disease has a clearly detectable and treatable precursor (adenomas), and early detection of CRC improves the prognosis. The five-year survival is 90% if the disease is diagnosed while still localized, only 68% for regional disease, and less than 10% for disseminated disease (Table 1).[30] In addition, Winawer et al. have clearly shown that endoscopic removal of adenomas results in a lower-than-expected incidence of CRC compared with reference populations.[31] Extensive, but mainly indirect evidence suggests that the majority of CRC arise from adenomas. However, only a minority of adenomas ultimately progress to CRC. Histopathology and size determine the risk on malignant transformation. The National polyp study workgroup introduced the concept of advanced adenoma defined as adenomas ≥10mm, or with a villous component of >25%, or containing high grade dysplasia [32] as all these factors appeared independent risk factors for the progression to CRC.[33] Furthermore, individuals with an advanced adenoma or more than two adenomas removed at screening turned out to be at increased risk for metachronous lesions when undergoing follow-up (surveillance) colonoscopy.[34-36] Several CRC screening studies therefore used the detection rate of invasive CRC, as well as advanced adenomas as surrogate end-point for the effectiveness of a screening tool, as randomised-controlled trials (RCT) evaluating mortality reduction of screening require a long term follow-up. Furthermore, stage distribution of detected CRC has been suggested as a surrogate end-point as well, given the significant difference in prognosis between early stage and dissimilated cancer (Table 1).

Table 1: Stage TNM classification 5-year survival.

Stage	T	N	M	Five year survival
I	T1–2	N0	M0	90%
IIA	T3	N0	M0	80%–85%
IIB	T4	N0	M0	70%–80%
IIIA	T1–2	N1	M0	65%–80%
IIIB	T3–4	N1	M0	50%–65%
IIIC	T1–4	N2	M0	25%–50%
IV	T1–4	N0–2	M1	5%–8%

Derived from Wolpin BM, Mayer RJ. Systemic treatment of colorectal cancer.(1)

Extensive evidence has shown that screening can reduce CRC related mortality. In 2003 the European Health Council recommended screening for CRC within the age group 50-75 years.[37] Unfortunately, only 43% of the target population in the European Union has nowadays access to population-based screening as part of a regional or national programme. In fact, in 2007 only 18% of the target population underwent adequate screening for CRC.[38] The International Colorectal Cancer Screening Network (ICRCSN) presented data on screening programmes worldwide. A few countries, including Finland, England, Scotland, Australia and several provinces in Canada have introduced a nation-wide call-recall screening programme. In France, Spain, Italy and Sweden, screening is offered at a regional level. Japan, Taiwan, USA, Germany, Poland, Czech Republic and Austria offer screening at an individual basis, also known as opportunistic programmes.[38] The Netherlands is currently considering introduction of a nation-wide screening programme.[39]

There are several methods for CRC screening, which vary in the level of supporting evidence, effectiveness, test-related burden and uptake. Screening tests can be divided in tests which primarily detect cancer, including guaiac-based faecal occult blood test (gFOBT), faecal immunochemical test (FIT) and faecal DNA test, and tests that can detect both polyps (adenomas) and CRC, like flexible sigmoidoscopy (FS), total colonoscopy (TC) and computed tomography colonography (CTC). The most commonly used tests; FOBT, FIT, FS, and TC are discussed in detail below. Less frequently used screening tests like faecal DNA testing and CTC will be discussed briefly.

SCREENING STRATEGIES

Guaiac-based faecal occult blood test (gFOBT)

Guaiac-based FOBT can detect occult blood based on the detection of haem in faeces, as it reacts to the peroxidase activity of haem. The standard protocol is a home-based test consisting of two samples each of three consecutive bowel movements. A positive test is followed by a TC. Most studies encouraged participants to restrict their diet and medication prior to performing the test as this might affect the number of false-positive and false-negative test results. The restrictions differ between studies, but generally involve avoiding red meat, fish, poultry, some fruits and vegetables, vitamin C, non-steroidal anti-inflammatory drugs (NSAID) and aspirin.[40-44] However, a meta-analysis did not find clear evidence for improved accuracy of the test when these dietary and medicine restrictions were applied [45], and a double-blind RCT did not find a relation between regular use of NSAIDs or aspirin and the number of false-positive test results.[46] Additionally, strict dietary and medication restrictions have been shown to lower uptake and should therefore not be advised in screening programmes.[47, 48]

The sensitivity and specificity of gFOBT screening varies widely due to the variation in type of test (brand), method of stool collection, number of stool samples per test, the use of rehydrated

stool samples, the threshold used for a positive test, and screening interval.[49, 50] Differences between test brands were shown in a systematic review, reporting that the sensitivity and specificity of a single test for detecting CRC was respectively 37.1% and 97.7% with unhydrated Hemoccult II testing and 79.4% and 87.7% with analysis by Hemoccult II Sensa.[49] Hydration of a faecal sample of a Hemoccult II improved the test sensitivity for CRC (50%), but reduced the specificity of the test (94%).[51] Rehydration of gFOBT slides is not recommended because it can negatively influence the interpretation of the test results and substantially increase the number of false-positive test results due a reduced specificity.[24] A single unhydrated gFOBT test thus has a low sensitivity and the majority of prevalent CRCs will be missed. Repeated screening is needed in order to obtain adequate programme sensitivity. Until recently a single sample in-office gFOBT performed by the general practitioner has been used for CRC screening especially in the United States. Collins et al. clearly demonstrated that this method has a considerable lower sensitivity and specificity than the home-based three sample gFOBT and is therefore not recommended.[52]

Guaiac-based FOBT can reduce mortality due to the detection of CRC at an early stage. Five randomised controlled longitudinal studies have consistently shown that gFOBT screening can reduce relative risk for CRC with 13%-33%.[53-57] A meta-analysis combined the results of the five RCT including 157 164 screenees and 156908 controls invited for biennial screening with 11-18 years follow-up and reported a 16% relative risk reduction of CRC-related mortality (RR 0.84 CI: 0.78-0.90).[58] In an individual study, the maximum risk reduction with annual gFOBT screening was 33%.[56] Today, both annual and biennial screening intervals are recommended.[24, 56, 59]

Attendance to screening is an important determinant of the effectiveness of a screening tool at a population level. The percentage of people attending the first round of gFOBT screening was between 49-68%.[58, 60] Attendance rates tend to be lower in successive screening rounds.[54] However, in the nation-wide call-recall British screening programme uptake levels remained stable over the first three screening rounds. Overall only 38% of the invitees persisted in their choice to attend screening over time and attend all screening rounds.[61] This implies, given the low sensitivity of a single gFOBT that only a small proportion of invitees receive adequate screening. Furthermore, uptake of gFOBT screening varies among subgroups within the target population. Women are more likely to participate than men. An age between 55-64 years is also associated with increased gFOBT uptake levels compared to younger (50-54) and older age groups (65-75).[61, 62]

Feacal immunochemical test (FIT)

Faecal immunochemical testing specifically detects human (haemo) globin by using mono- or polyclonal antibodies. Globin is the protein component of haemoglobin. The antibodies are attached to latex, dye or enzymes, which form complexes in presence of globin that can be detected. The degree of agglutination, turbidity or colour change of the solution is read as an optical change and translated to a concentration of haemoglobin per amount of faeces or sample solution. Dietary restrictions are not required as FIT specifically detects human (haemo)

globin, without any cross-reaction with dietary haem. The use of NSAID's, aspirin, or anticoagulants slightly improves the sensitivity of FIT without a reduction in specificity for the detection of advanced adenomas and CRC.[63] The limited effect of medication and dietary restrictions on test accuracy and a potential negative effect on participation rate make medication and dietary restrictions unwarranted.[48, 64]

Faecal immunochemical tests are more sensitive than gFOBT for detection of haemoglobin (Hb) in faeces.[49] FIT can be analysed quantitative and non-quantitative. For the latter method, faeces can be collected on a card containing anti-human Hb which forms a complex with faecal Hb which binds in a positive test reaction zone producing a coloured line, which can be analysed by a reader. This non-quantitative method is not suitable for population-based screening as the analysis is laborious and subject to inter-observer variability. Therefore quantitative faecal immunochemical tests have been developed with various types available including OC-sensor (Eiken Chemical Co., Tokyo, Japan), Hem-SP (Fujirebio, Japan) and FOB Gold (Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy). With these techniques, FIT samples can be analysed automatically which has important advantages for reproducibility, quality control, capacity, and thus personnel need and costs.[50, 65] Another advantage is the quantitative test result, which allow determining an optimal cut-off value for a nation-wide screening program.[65-70] For the OC-sensor a cut-off value between 75-100ng/ml seems most favourable as they provide an optimal balance between detection rate and predictive values,[65, 69, 71, 72] whereas cut-off levels of respectively 20ng/ml [73] and 100ng/ml [74] for the Hem-Sp and the FOB-gold have been suggested. Countries implementing nation-wide screening can decide on the cut-off value based on a positivity rate that meets the available colonoscopy resources in a country. At the same time, the number of colonoscopies is an important determinant of the neoplasia detection rate, and thus of the potential preventive effect of a CRC screening programme.

The number of consecutive bowel movements collected for a single screening round varies between one and three samples. The two- or three sample FIT has a higher sensitivity for detecting CRC than a single FIT.[65, 75-77] A single test has a sensitivity and specificity for detecting advanced neoplasia of respectively 27% and 95% [73], and a two or three samples test of 67% and 87-94%.[65, 70] Li et al. postulated that two consecutive stool samples is a more cost-effective approach than three-sample, as both strategies demonstrated similar sensitivity and specificity. However, randomised population-based trials on the optimal number of consecutive stool samples are awaited. In general a two or three sample FIT is considered positive when one of the samples is above a certain threshold level. Recently, Guittet et al. showed that the best gain in sensitivity and specificity is obtained when the mean Hb levels of both tests are used.[75]

Definitive evidence on the effectiveness of FIT screening is lacking. A small Japanese case-control study suggested that repeated screening by FIT would reduce mortality from colorectal cancer by 52-60%. Two randomised trials consistently showed a higher detection rate and similar number of false-negatives for FIT compared to gFOBT.[69, 72] FIT therefore seems

a more effective screening tool and may reduce CRC-related mortality considerable more than reported for gFOBT screening.

Participation rates tend to be higher for FIT compared to the gFOBT (60-62% vs. 47-50%).[62, 78] This may be influenced by the differences in perceived discomfort, the number of faecal samples required and the difference in faecal sampling method.

Flexible sigmoidoscopy (FS)

Flexible sigmoidoscopy is an endoscopic technique that examines the distal part (rectum, sigmoid and descending colon) of the colon. The procedure is usually performed with a forward-looking video endoscope (usually 60–70 cm). The goal of FS is to examine the colon as far as can be achieved to the limits of FS endoscope length and without causing undue pain or distress.[79] A single, self-administered, enema is used as bowel preparation in most population-based screening studies.[62, 80-82] Self-administration of the enema at home has been shown to be acceptable, as a minority of participants refuses self-administration and receives the enema at the screening unit.[62, 80] This is important for FS screening, because most screening units lack facilities to apply all enemas. A single self-administrated enema resulted in adequate bowel cleansing (when lesions ≥5 mm polyps are not obscured)[79] in 93-95%.[80, 83] In the remaining subjects oral laxatives combined with an enema can be considered, as this combination has demonstrated improved preparation quality [84, 85].

FS is in general performed without sedation and can therefore be performed in an office setting. In such a setting, only a small proportion of participants report severe embarrassment, discomfort or pain during the procedure.[80, 83, 86, 87] The majority of subjects are willing to return for successive screening rounds.[86-89] This is essential for an effective screening programme, since screening tests must be repeated at regular intervals. Furthermore, experience with CRC screening will be communicated to other potential screenees, which may influence participation. Perceived burden of FS screening varies by gender. Women report significantly more burden than men and are therefore less willing to return for successive screening rounds.[89] Endoscopists should therefore be even more aware of potential pain in women, and consider protective action (e.g. using sedation or a more flexible, smaller calibre endoscope). Male endoscopists are reported to be a barrier to screening for women.[89] A nation-wide screening programme might be more effective when female endoscopists take part in FS screening.

FS is considered a rather safe procedure. Serious complications like bleeding following polypectomy or perforation occur in 1-2 per 1000 screenees.[80, 82]

The criteria to refer a participant for a TC are still under debate. Subjects with three or more adenomas or advanced neoplasia are at increased risk of synchronous proximal advanced neoplasia. [90-93] Most studies therefore considered a FS positive in case of an advanced adenoma, ≥ 3 adenomas; or invasive CRC.[62, 82, 83] Subjects with polyps sized ≥10 mm are usually also referred for TC.[62, 94] A lower referral threshold size for distal adenomas (5mm) does not appear to considerably increase the yield of proximal advanced adenomas and is therefore not recommended.[82]

FS screening has the potential to reduce CRC related mortality based on both endoscopic removal of adenomas and the early detection of CRC. Case-control studies reported a CRC mortality reduction of 59-79% within the reach of the endoscope following a single FS. Recently, a Norwegian population-based RCT reported the effect of a single FS on CRC incidence and mortality after seven years. [95] The intention-to-screen analysis demonstrated no difference in the seven year cumulative incidence of CRC or CRC-related mortality between the screening and control group. However, prevalent CRCs detected at the first screening round diluted any incidence reducing effect of polypectomy. It may take longer than seven years to determine the effectiveness of FS screening on CRC incidence. For those actually attending screening a significant reduction in CRC related mortality was apparent (hazard ratio 0.41, CI 0.21-0.82, P=0.01). The longitudinal results of three larger RCTs performed in the United Kingdom, United States and Italy are expected in the near future.[82, 94, 96]

Further evidence on the effectiveness of FS comes from TC studies. Examination of the distal colon, followed by a TC if an adenoma of any size had been found, would have identified 66-80% of all subjects with an advanced neoplasia.[91, 97] FS seems a less effective screening tool in women than in men as the detection rate of advanced adenoma is approximately 35% compared to 66% in men.[98] Furthermore, increasing age is also associated with a higher miss rate of advanced neoplasia in the proximal colon.[98]

Limited evidence on the optimal screening interval after a negative examination is available. Case-control studies found that the negative association between FS and CRC-related mortality persisted for up to 6-10 years.[99-101] More recent data provided direct evidence to support the safety of the five-year interval after a normal FS, as the detection rate of advanced neoplasia five-year after a negative FS is only 1%.[102, 103] Current guidelines therefore recommend at least a five-year interval in presence of high quality FS.

The quality of the examination determines the effectiveness of FS screening. Although longitudinal data on the association between adenoma detection rate and mortality reduction are lacking, the detection rate of adenomas has been suggested to be a surrogate marker for the quality of examination.[104] The detection rate varies widely between endoscopists irrespective of the level of experience. Individual performances of an endoscopist thus also contribute to difference in detection rate. Atkin et al. suggested that a high quality FS program should achieve an adenoma detection rate of at least 10% for screening FS in an average risk population over 55 years of age.[104]

The participation rate to FS screening differs between countries (24-67%).[62, 81, 105, 106] These uptake rates cannot be directly compared to studies where only eligible and interested respondents to a questionnaire were included.[82, 94] Differences in attendance rate can partly be explained by the method of scheduling the FS appointment. In some studies subjects were asked to schedule their own appointment, which may negatively influence the participation rate.[62] In other studies the appointment for FS was prefixed to be confirmed or modified.[81, 82, 94] Women are less likely to attend FS screening than men, which may be influenced by attitude

and believes about FS screening that might thereby form a barrier to FS screening. [62, 82, 94, 105, 106] A special approach for inviting women in a future nation-wide FS screening programme should therefore be considered.

Total colonoscopy (TC)

Total colonoscopy is considered the golden standard for the detection of colorectal neoplasia. A colonoscopy is performed with a forward-looking colonoscope. The scope should be advanced until the caecum has been reached. Bowel preparation is in general performed with polyethylene glycol (PEG) or sodium phosphate.[97, 98, 106, 107] A meta-analysis demonstrated no significant differences in efficacy between both preparations.[108] Sodium phosphate is better tolerated than PEG, but associated with an increased risk of clinically significant electrolyte disturbances.[108]

Colonoscopy is well accepted under conscious sedation.[86, 89] The bowel preparation is often considered the worst part of the procedure.[89] Clinically significant complications requiring hospitalisation occur in 1 per 1000 screenees including perforation and bleeding.[109] In a large population-based colonoscopy screening trial no mortality within 30 days of the colonoscopy was reported.[107]

Randomised controlled data on the preventive effect of a colonoscopy on CRC incidence and/or mortality are lacking. The National Polyp Study estimated a 76-90% reduction of CRC incidence by regular colonoscopic surveillance examinations.[110] However, these results should be interpreted with caution. The two reference groups in this study were derived from different populations, which could introduce a selection bias. Furthermore, all subjects included in this trial had a polyp removed at the index colonoscopy and were therefore at increased risk of CRC. The results of this trial can therefore not be extrapolated to an average risk screening population. Recently a large case-control study executed in Canada including average risk men and women showed that colonoscopy was associated with lower CRC mortality rates (OR 0.69; CI 0.63-0.74). This study suggested that colonoscopy screening predominantly affects left-sided CRCs as no preventive effect on right-sided CRC was observed.[111] The lack of protection for the right colon is most likely due to the use of billing codes without actual evaluation of endoscopy reports and pictures. Furthermore, poor bowel preparation or inadequate withdrawal time in the right colon might also increase the miss rate of right-sided polyps and therefore lowering the effect on CRC-related mortality. Furthermore, adenomas in the right-sided colon are more likely to have a flat morphology, and therefore more likely to be missed at colonoscopy.[112] These flat adenomas more frequently contain highly malignant characteristics (high-grade dysplasia)[113] suggesting a more aggressive pathway in the development of flat adenomas to CRC.[114] However, RCT to determine effectiveness of colonoscopy on CRC-related mortality are required to confirm the data of Baxter et al.

Colonoscopy allows for full examination of the colon. Polyps can nevertheless be missed.[115, 116] A meta-analysis on tandem colonoscopy studies reported an association between polyp size and miss rate as adenoma miss rate increased significantly with smaller size from 2% for

large adenomas (≥10 mm) to 13% for small adenomas (6–9mm), and to 26% for diminutive adenomas (1–5 mm).[116]

Attempts should be made to reduce the polyp miss rate and therefore the effectiveness of TC screening. Rex et al. have summarized evidence on quality indicators for TC. A high quality screening colonoscopy depends on: (i) an appropriately trained and experienced endoscopist; (ii) obtaining informed consent, including a specific discussion of risks associated with colonoscopy; (iii) adequate bowel preparation and visualisation of the colon; (iv) caecal intubation in ≥95% of cases; (v) mean withdrawal time of more than six minutes in TC with normal results performed in patients with intact anatomy [117]; (vi). adenoma detection rate of ≥25% in average risk men and ≥15% in average risk women aged 50 years or older in a first colonoscopy (vii) documentation of perforation and post-polypectomy bleeding, which should be observed in less than respectively 0.1% and 1.0%; (vii) recommendations for surveillance or repeat screening based on published guidelines.[25]

Indirect evidence from a case-control study suggested a very low risk of CRC for 20 years after a negative colonoscopy.[118] Prospective studies provided evidence for a protective effect of at least five years after a negative colonoscopy.[34, 119] Recently, Brenner et al. reported a low risk on advanced adenoma for at least fifteen years after a negative colonoscopy.[120]. The current guideline recommends a ten year screening interval although lengthening of the interval might be considered.[24]

Uptake rate of colonoscopy screening is approximately 25% when a call-recall approach is applied.[106, 121]

Faecal DNA test

During the adenoma carcinoma sequence DNA alterations accumulate. Adenomas and CRCs continuously shed mucosal surface cells into the faeces. The DNA material from these cells can be isolated and analysed by means of a multi-target DNA stool assay. By this means, tests usually aim to detect mutations in TP53, K-ras, APC, BAT-26 and BRAF. In contrast to FOBTs, sDNA tests require an entire stool specimen (30g minimum) to ensure adequate sample of stool for evaluation.

An American study with 5486 asymptomatic subjects showed increased sensitivity and specificity for advanced neoplasia using faecal DNA compared to gFOBT. DNA testing nevertheless missed more than 50% of the advanced neoplasia.[122] Recently a cost-effectiveness analysis using a Markov model demonstrated that immunochemical and guaiac-based tests are to be preferred over DNA testing.[123]

The U.S. Preventive Services Task Force (USPSTF) concludes that there is insufficient evidence to assess the sensitivity and specificity of faecal DNA testing for colorectal neoplasia, and that therefore the balance of benefits and harms cannot be determined for this test.[124] Further research is required before implementing a nation-wide screening programme with faecal DNA testing.

Computed Tomography Colonography (CTC)

Computed Tomography Colonography is able to visualise the entire colorectum. Currently a ≥16 slice scanner is most commonly used in studies on CRC screening. This technique allows a 2- and 3-dimentional visualisation of the colon. Cathartic preparation along with a liquid diet the day prior to the CTC, similar to the preparation of TC, is required to obtain adequate visualisation of the colon. Subjects report bowel preparation to be the most important drawback to participating CRC screening.[125] Therefore, a less burdensome limited bowel preparation using faecal tagging has been introduced.[126] This rapidly evolving technique has an adequate sensitivity, which is only slightly lower than seen with cathartic cleansing.[126]

International experts agree on the referral of subjects with polyps ≥10mm for a TC. The debate regarding the referral of subjects for TC relates to subjects with small polyps (6-9mm) as most advanced lesion. Pickhardt et al. concluded in an extensive review that, based on a low miss rate of advanced neoplsia and an substantial increase of the cost-effectiveness, subjects with small polyps should have a surveillance CTC after three years.[127] Subjects with diminutive polyps or a normal CTC are recommended to be screened with a five year interval.[24]

The complication rate of CTC is considerably low, with a serious perforation in 1 per 3000 subjects.[128] The dose of radiation as used for CTC screening in a 50 year old individual is estimated to increase the risk on CRC with 0.044% and all cancers with 0.14%.[129] Furthermore, the CT can detect extra-colonic findings in a considerable number of screenees. In approximately 10% of subjects the extra-colonic findings are clinically relevant and require evaluation or intervention, which will increase the costs of a screening programme.[130]

The sensitivity achieved with CTC for the detection of advanced adenomas is highly dependent on the skills of the reader.[131] A pooled per patient analysis reported an average sensitivity and specificity for subjects with large polyps (≥10mm) of respectively 93% (CI 73-98%) and 97% (CI 95-99%). The sensitivity and specificity decreased to respectively 86% (CI 75-93%) and 86% (CI 76-93%) when small polyps (6-9mm) were included. However, this per patient analysis clearly did not provide insight in the performance of the CTC per individual polyp. The sensitivity was significantly lower when a per polyp analysis was performed, with a sensitivity of 77% (CI 70-83) for large polyps and 70% (CI 63-76%) for polyps ≥6mm.[132]

A limitation of all studies on CTC screening is the use of TC as golden standard, since the sensitivity of the TC for the detection of advanced neoplasia is not 100%. No randomised controlled trials on the efficacy of CTC for prevention of CRC have been performed. Studies on CTC mainly use the detection of advanced neoplasia as surrogate end-point for efficacy. Recently USPSTF concluded that evidence to assess the harms related to extra-colonic findings of CTC is insufficient, and the balance of benefits and harms cannot be determined.[124] More extensive research is needed until CTC can be used as a screening strategy in an average risk population.

STARTING AND STOPPING AGES FOR SCREENING

Screening for CRC with gFOBT, FIT, FS or TC should be initiated at the age of 50 in an average risk population.[24, 37, 133] The higher incidence of CRC before the age of 50 in African Americans warrant initiation of CRC screening in this group at the age 45 rather than 50 year.[134] Furthermore, clinicians might consider offering screening at a younger age to heavy smokers, as they are at increased risk for CRC. The USPSTF recently recommended to continuing screening until age 75 years.[124]

CONCLUSIONS

The various test methods available for CRC screening have been shown to be feasible for CRC screening. However, the tests differ in the level of supporting evidence, reducing effect on CRC related mortality, potential risks and test burden. In the Netherlands gFOBT, FIT and FS are considered as potential screening tests for a nation-wide screening programme.

AIMS OF THE THESIS

The general aim of this thesis is to explore all aspects (i.e. participation, diagnostic yield, test burden, preference for a test, cost-effectiveness) of the three most relevant screening tests in a European setting, i.e. gFOBT, FIT and FS with regard to implementation of a nation-wide call-recall screening programme in the Netherlands.

OUTLINE OF THE THESIS

Introduction of a CRC screening program in the Netherlands is being explored. The benefits of screening depend on the efficacy and costs of the screening method as well as on population attendance. The currently most relevant screening methods for the Netherlands are gFOBT, FIT and FS, with the latter being more expensive but also with potentially higher preventive impact. In this thesis, we firstly determined attendance for and detection rates of advanced neoplasia with gFOBT, FIT and FS screening in a randomised population-based trial (Chapter 2).

FIT samples can be analysed automatically which has important advantages for reproducibility, quality control, capacity, and thus personnel need and costs. Another advantage of FIT is the quantitative test result, which allows determining of an optimal cut-off value for a nation-wide screening program. The cut-off value for a positive test can be based on a positivity rate that meets the available colonoscopic resources. At the same time, the number of colonoscopies is

an important determinant of the neoplasia detection rate, and thus of the potential preventive effect of a CRC screening programme. We therefore determined the optimal cut-off value of the FIT (OC-Sensor micro) in an average risk screening naïve Dutch population (chapter 3).

Uptake of FS screening is low in various European populations. A significant proportion of the population would therefore not receive any screening if a single test population-based screening programme based on FS would be introduced. Several surveys have identified worries about pain, discomfort, or injury associated with FS screening as the main reasons for refusing FS screening. Those barriers may be overcome by offering non-participants an alternative screening test, for example FIT. We determined uptake and diagnostic yield of FIT screening among non-participants of FS screening in an average risk screening naïve population (chapter 4). This approach allowed insight in reasons for non-compliance to FS screening.

Experience with a screening test may affect the willingness to attend successive screening round, and may be communicated to other potential screenees, which may affect uptake of CRC screening programmes in successive cohorts. A few studies have reported on the test burden of gFOBT and FIT screening. The perceived test burden of FS screening has been more widely studied, but trials comparing the burden of gFOBT, FIT and FS screening are lacking. In this thesis, we assessed differences in perceived burden and willingness to return for a second screening round among participants of a randomised population-based trial comparing gFOBT, FIT and FS screening (chapter 5).

The willingness to undergo screening is influenced by perceived advantages and drawbacks of CRC screening tests and furthermore, by knowledge and awareness of CRC, CRC risk and CRC screening. To optimise a CRC screening programme it is of paramount importance to gain insight in factors that influence population preferences for CRC screening programmes, and the trade-offs individuals are willing to make between benefits and drawbacks of a CRC screening programme. Research has shown that patient preferences can have a major impact on their willingness to use services and furthermore, there is an increasing emphasis on involvement of patients in health care decisions. We therefore investigated preferences for CRC screening using a labelled (chapter 6) and an unlabelled (chapter 7) discrete choice experiment (DCE). DCE is a survey methodology with its origin in market research. DCEs are widely used for the assessment of preferences in transport and environmental economics and marketing research. They are increasingly used for investigating health care preferences.

Advanced adenomas are considered the surrogate biological marker for CRC risk and are the primary target of screening. Accurate pathologic assessment of colorectal lesions is therefore of paramount importance. However, concern has been expressed about the reproducibility of the histological interpretation, even between expert pathologists. As a limited reproducibility has a major influence on intensity, burden, cost-efficacy, and potentially outcome of CRC screening, we reported the inter-observer variation in the histological diagnosis of colorectal polyps detected in a CRC screening programme. Furthermore, the inter-observer variation between general and expert pathologists was assessed (chapter 8).

All the longitudinal randomised controlled FOBT trials on mortality reduction have been performed with the Hemoccult II test. These trials took many years before showing their final results. It is not be feasible to subject the FIT to such a trial within the time frame of this thesis. As a proxy, we therefore used a model-based analysis (MISCAN-Colon model) to estimate expected effects and costs given the differences in characteristics based on data of our randomised trial comparing gFOBT and FIT (chapter 9). The MISCAN-Colon model is structured in such a way that an assumed change in specificity and/or sensitivity is translated into a change in stage distribution, in types of treatments, in overall prognosis and thus in mortality.

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Chapter 2

Screening for colorectal cancer; randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy

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ABSTRACT

Screening for colorectal cancer (CRC) is widely accepted, but there is no consensus on the preferred strategy. We conducted a randomised trial comparing participation and detection rates (DR) per screenee of guaiac-based faecal occult blood test (gFOBT), immunochemical FOBT (FIT), and flexible sigmoidoscopy (FS) for CRC screening. A representative sample of the Dutch population (n=15011), aged 50-74 years, was 1:1:1 randomised prior to invitation to one of the three screening strategies. Colonoscopy was indicated for screenees with a positive gFOBT or FIT, and for those in whom FS revealed a polyp with a diameter ≥10 mm; adenoma with ≥25% villous component or high grade dysplasia; serrated adenoma; ≥3 adenomas; ≥20 hyperplastic polyps; or CRC. The participation rate was 49.5% (95% confidence interval (CI) 48.1-50.9%) for gFOBT, 61.5% (CI:60.1-62.9%) for FIT and 32.4% (CI 31.1-33.7%) for FS screening. gFOBT was positive in 2.8%, FIT in 4.8% and FS in 10.2%. The DR of advanced neoplasia was significantly higher in the FIT (2.4%; OR 2.0; CI 1.3-3.1) and the FS arm (8.0%; OR 7.0; CI 4.6-10.7) than in the gFOBT arm (1.1%). FS demonstrated a higher diagnostic yield of advanced neoplasia per 100 invitees (2.4; CI 2.0-2.8) than gFOBT (0.6; CI 0.4-0.8) or FIT (1.5; CI 1.2-1.9) screening. This randomised population-based CRC-screening trial demonstrated superior participation and detection rates for FIT compared to gFOBT screening. FIT screening should therefore be strongly preferred over gFOBT screening. FS screening demonstrated a higher diagnostic yield per 100 invitees than both FOBTs.

BACKGROUND

Screening can reduce the colorectal cancer (CRC) mortality rate based both on early detection of CRC and endoscopic removal of adenomas.[1, 2] CRC screening is therefore widely accepted, but there is no consensus on the preferred strategy. The European Council recommends faecal occult blood (FOBT) screening CRC in average risk men and women aged 50–74 years.[3] More than 50% of the target population in the European Union is however offered no screening at all. In those regions where screening is being offered, this usually occurs with guaiac-based FOBT (gFOBT) or more rarely with flexible sigmoidoscopy (FS).

Four large randomised controlled trials (RCT) have consistently shown that biennial gFOBT screening reduces CRC mortality.[4-7] This reduction mainly occurs due to early detection of CRC. However, gFOBT is hampered by a low sensitivity for advanced neoplasia (11-37%), which explains the limited impact of repeated gFOBT screening on CRC mortality.[8, 9] Recently, immunochemical FOBT (FIT) screening has become available. FIT has a better sensitivity and similar specificity for detecting advanced neoplasia compared to the gFOBT, since it specifically detects human haemoglobin.[8, 10-15]

Sigmoidoscopy screening is possibly more effective than FOBT screening due to the considerable higher sensitivity for detection of early neoplastic lesions and the possibility of removing adenomas during the screening procedure.[16, 17] Case-control studies reported a CRC mortality reduction of 59-79% within the reach of the endoscope following single FS.[18, 19] The results of RCTs on mortality reduction of FS screening are expected in the near future.[20-23]

In addition to mortality reduction, uptake of screening is the second major determinant of effectiveness of a CRC screening programme. Until now, randomised trials directly comparing the three most relevant screening methods in an unselected asymptomatic population are lacking. We therefore conducted a randomised population-based trial to compare gFOBT, FIT and FS screening in an average risk screening naïve population. The primary endpoint of this study was the participation rate to each of the three screening strategies. Detection rate (DR) of advanced neoplasia with each screening strategy was the secondary aim.

METHODS

Study population

Names, dates of birth, and postal addresses of all individuals aged 50-74 years in the region Rijnmond in the Southwest of the Netherlands were obtained from the eight regional municipality offices. From this dataset of 338000 individuals, a random sample of 15011 individuals was taken by computer generated algorithm and 1:1:1 randomised using this computer generated algorithm (Tenalea, Amsterdam, the Netherlands). Randomisation was done per postal address after stratifying by age, sex and social economic status (SES) into group A (gFOBT), B (FIT) or

C (FS) (Fig 1). The SES was based on the data of Statistics Netherlands (www.cbs.nl) providing average SES per postal code area, each representing small neighborhoods). Randomisation occurred prior to invitation. Informed consent was asked after randomisation. Individuals with a history of inflammatory bowel disease or CRC, a colonoscopy, sigmoidoscopy or barium contrast enema in the last three years, major health problems, or those who moved away or died were excluded from analyses. Recruitment took place between November 2006 and November 2007.

Interventions

All individuals were sent a pre-invitation letter containing information on CRC screening. Two weeks later an invitation letter was sent with information on possible advantages and risks of screening and on the specific screening test that was offered. This was accompanied by an informed consent form, which had to be signed and returned. A test set was sent along with the invitation in case of gFOBT or FIT screening. The FS group received an invitation letter with a telephone number of the screening unit to schedule an appointment. A reminder was sent six weeks afterwards to all non-respondents. Information about the study was further given to all general practitioners (GP) in the region by direct visits of research physicians prior to start of the study, providing them with background, a contact address, and an information folder. All information was made available via a dedicated website (www.dikkedarmkankerpreventie.nl), mailings and information sites of the municipality offices, regional newspapers and national and regional broadcasting.

Group A: Guaiac-based FOBT

All randomised individuals received three guaiac imprinted test cards at invitation (Hemoccult II, Beckman Coulter Inc., Fullerton USA) to be used on three consecutive bowel movements without dietary restrictions or medication limitations. Participants returned the test kit by mail to the Gastroenterology and Hepatology laboratory of the Erasmus Medical Centre. Tests were analysed without re-hydration. A test was considered positive if one or more panels were positive. A digital picture of the test cards was taken and stored in a database. A subset of 241 photographs was re-evaluated by a second technician blinded for the initial test results. A third technician reviewed the tests in case of inter-observer variation.

Group B: Immunochemical FOBT

Subjects received one immunochemical FOBT kit (OC-Sensor micro, Eiken Chemical Co., Tokyo, Japan) to collect a single faecal sample of one bowel movement. Participants returned the test kit by mail to the same laboratory as mentioned above for quantitative analysis using the automatic OC-sensor μ instrument (Eiken Chemical Co., Tokyo, Japan). The test was considered positive above a cut-off value of 100 nanogram haemoglobin/ml according to the instructions of the manufacturer and in agreement with previous studies using the same test.[24, 25]

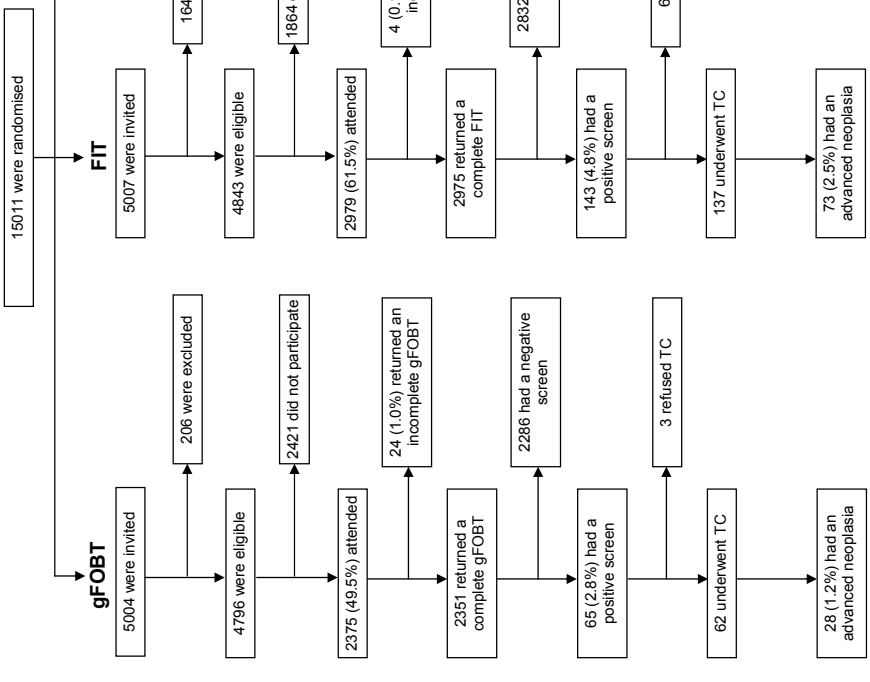

Fig 1: Trial profile.

Group C: Flexible sigmoidoscopy

Individuals randomised to FS, once scheduled for an appointment, received a 120ml phosphate enema (Clyssie, B. Braun Medical B.V., Oss, The Netherlands) by mail with instructions for self-administration. Administration of the enema by a nurse in the screening unit was offered as an alternative. Flexible sigmoidoscopy was performed with a regular forward-looking video-colonoscope (Olympus Europe, Hamburg, Germany). All sigmoidoscopies were performed by experienced endoscopists (>200 colonoscopies) in a dedicated screening centre. The endoscope was advanced as far as could be achieved without causing undue pain or distress aiming to reach the splenic flexure. The FS was considered complete when the endoscope was advanced beyond the colon descending–sigmoid junction into the proximal descending colon and more than 50 cm of the anal verge with endoscope in straightened position. Participants did not receive sedatives. The reach of the endoscope in straightened position was recorded in cm and location, as was the adequacy of bowel preparation. If bowel preparation was inadequate, the participant was offered an additional enema in the screenings unit followed by repeated FS during the same appointment, or to schedule a new appointment with oral bowel preparation (Prunacolon 75 ml) in combination with an enema. During FS, characteristics including size, and location of all polyps were noted and recorded. The size of each polyp was measured using an open biopsy forceps with 7mm span. All polyps up to a diameter of 9 mm were removed at FS and sent for histological evaluation. Polyps with a diameter of ≥10 mm were left in situ for removal during colonoscopy. Participants were referred for colonoscopy when one of the following criteria was met: presence of a polyp with a diameter ≥10 mm; an adenoma with serrated, villous histology (≥25% villous) or high-grade dysplasia; ≥3 adenomas; ≥20 hyperplastic polyps; or invasive CRC.[22] In accordance with the international classification, CRC was defined as the invasion of malignant cells beyond the muscularis mucosa. One experienced gastrointestinal pathologist evaluated all samples. A second gastrointestinal pathologist evaluated a subset of 50 adenomas and all advanced neoplasia.

Test results

In case of a positive gFOBT, FIT or FS the GP was informed by telephone and mail within two weeks. The GP informed the participant about the test result and referred the participant for colonoscopy. A colonoscopy was scheduled within four weeks after the screening test results had become available. Participants with a negative gFOBT or FIT and participants with no or low-risk polyps at FS were informed by mail within two weeks.

Ethical approval

The study was approved by the Dutch Ministry of Health (2006/02WBO). The approval included the pre-randomisation design. The study letters and information brochures were approved by the Institutional Review Board of the Erasmus Medical Centre (MEC-2005-264).

Power calculation

The primary outcome measurement was the participation rate. The sample size was chosen based on a presumed overall 50% participation rate to yield an 80% power to discern a 2.0% difference in participation between the three screening strategies and a 2.5% difference in participation between a maximum of three equal-sized subgroups per arm.

Statistical analysis

Differences in proportions between screening strategies were calculated using the χ^2 test. Differences in means between screening strategies were calculated using a Student t-test. The participation rate was calculated by dividing participants by all eligible subjects (defined as all randomised subjects minus the excluded subjects). An univariate logistic regression model was fitted to the data to determine differences in participation rate between the three screening strategies. Separate uni- and multivariate models were fitted to the three screening arms with participation as function of age, sex, SES and rural vs. urban domicile. Interaction of age and sex was determined using a multivariate model for each screening arm. A significant interaction was found in the gFOBT arm between age and sex on participation (p=0.009). Age and sex-specific participation rates to gFOBT screening were therefore presented in the result section. The DR was defined as the proportion of screenees with advanced neoplasia. This definition included subjects with CRC, and those with advanced adenomas. Advanced adenoma was defined as adenoma ≥10 mm, with a villous histology (≥25% villous) or with high-grade dysplasia. The DR was calculated using the most advanced lesion detected per screenee. A multivariate logistic regression model with advanced neoplasia or CRC as a function of age, sex and screening test was used to determine the differences in DR between screening tests. The diagnostic yield per 100 invitees was calculated as subjects with an advanced neoplasia or CRC divided by all eligible subjects. All p-values were two-sided and considered significant if <0.05.

RESULTS

Participation

Of the 15011 subjects who were randomised prior to invitation to one of the three tests, 670 were excluded from analysis (4.5%; 608 subjects met one of the exclusion criteria, 43 had moved away and 19 had died). The overall participation rate was 48.0% (CI 47.1-48.7%). In total 49.5% (CI 48.1-50.9%) attended gFOBT, 61.5% (CI 60.1-62.9%) FIT and 32.4% (CI 31.1-33.7%) FS screening (Fig 1).

In univariate analysis sex, age, SES and rural versus urban domicile were associated with participation rate in all screening arms (all p<0.05) (Fig. 2). Multivariate analysis showed indication between sex and age on participation in the gFOBT arm (p=0.009). The age-specific participation

rate to gFOBT screening was significantly higher in women than in men aged 50-59 years (OR 1.6; CI 1.4-2.0), while no difference between both sexes was seen in the age groups 60-64 (OR 1.1; CI 0.9-1.4) and 65-74 (OR 1.0; CI 0.8-1.2). The participation rate of men aged 50-59 was significantly lower than men aged 60-64 years (OR 0.8; CI 0.7-1.0; $p<0.05$). Participation rates were similar for the different age groups in female invitees to gFOBT screening. Independent predictors for higher participation to FIT screening were female sex, and age 60-64 years. Male sex and age 60-64 years were independent predictors for a higher participation to FS screening. Living in a rural area and a high SES were associated with a higher participation rate in all three screening arms (Table 1).

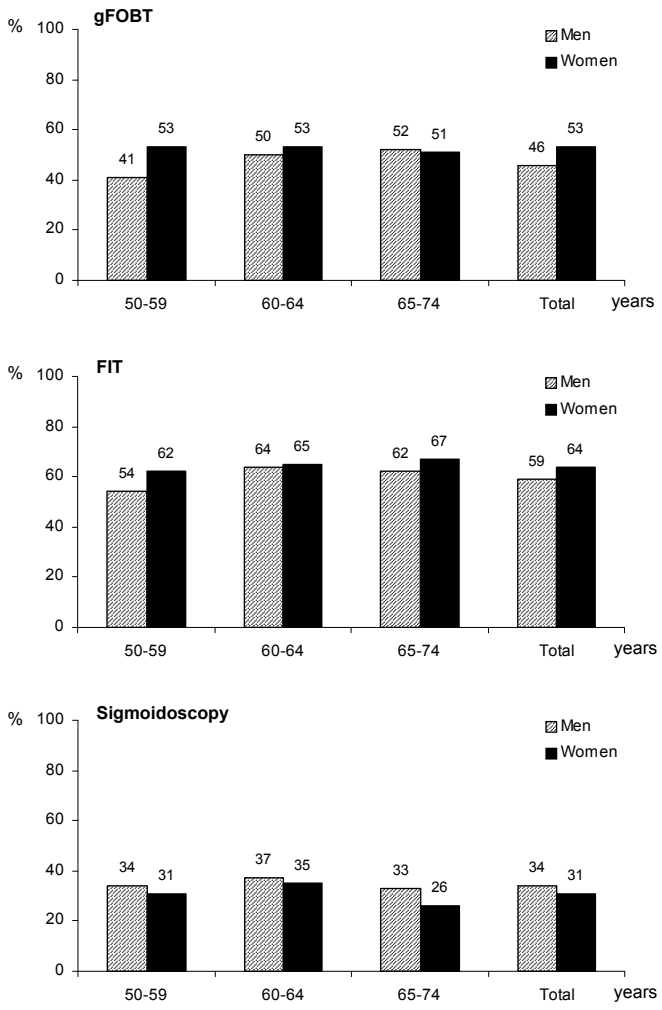

Fig 2: Age specific participation rates to guaiac-based faecal occult blood test (gFOBT), immunochemical faecal occult blood test (FIT) and flexible sigmoidoscopy (FS) screening of men and women

Table 1: Participation rate by age, gender, social economic status and rural versus urban in all screening arms; multivariate analysis.

	gFOBT OR (CI)	FIT OR (CI)	FS OR (CI)
Men	1	1	1
Women	1.1(0.9-1.4)‡	1.3 (1.1-1.4)*	0.9 (0.8-1.0)*
50-59yr	0.8 (0.7-1.0)‡*	0.8 (0.7-0.9)*	0.9 (0.7-1.0)*
60-64yr	1	1	1
65-74yr	1.0 (0.8-1.2)‡	1.0 (0.8-1.2)	0.8 (0.6-0.9)*
SES low	1	1	1
SES middle	1.2 (1.1-1.4)*	0.9 (0.8-1.1)	1.0 (0.8-1.2)
SES high	1.1 (1.0-1.3)	1.3 (1.1-1.5)*	1.2 (1.0-1.4)*
Strong urban	1	1	1
Urban	1.7 (1.4-2.1)*	1.2 (1.0-1.5)	1.2 (1.0-1.5)
Rural	2.6 (1.9-3.6)*	2.3 (1.6-3.3)*	1.8 (1.3-2.6)*

ORs adjusted for all the other variables in the table;
‡ Interaction of age and sex in gFOBT arm. Therefore age-specific OR (60-64yrs olds) are presented for men and women and sex specific ORs (male) for the different age groups.
* P<0.05;

Screening strategies

GFOBT was analysable in 2,351 cases (99%), and was positive in 65 cases (2.8%). Sixty-two (95%) subjects underwent a colonoscopy, which was complete in all cases. Advanced adenomas were found in 22 (0.9%), and a CRC in six screenees (0.3%) (Table 2). Of the six CRCs, three (50%) were classified as early stage (stage I 1, stage II 2) and three (50%) as advanced CRCs (stage III 2, stage IV:1). The positive predictive value (PPV) of gFOBT was 45.2% for an advanced neoplasia and 9.7% for a CRC.

FIT was complete in 2975 subjects (99.9%). A cut-off value of 100ng/ml resulted in 143 (4.8%) positive tests. In total 137 (96%) of the positive screenees underwent colonoscopy. This procedure was complete in 134 (98%) subjects. A double contrast barium enema was performed in one subject with an incomplete colonoscopy. Advanced adenoma were detected in 59 (2.0%)

Table 2: Most advanced lesion identified by screening.

N (%)	gFOBT	FIT	FS*
Completed screening test	2351	2975	1386
Positive screening tests	65 (2.8)	143 (4.8)	142 (10.2)
Colonoscopy performed	62 (95)	137 (96)	141 (99)
Detection rate			
Non-neoplastic polyp	4 (0.2)	7 (0.2)	272 (19.6)
Non-advanced adenoma	12 (0.5)	23 (0.8)	183 (13.2)
Advanced adenoma	22 (0.9)	59 (2.0)	103 (7.4)
Colorectal cancer	6 (0.3)	14 (0.5)	8 (0.6)
Positive predictive value			
Advanced adenoma	35.5	43.1	n.a.
Colorectal cancer	9.7	10.2	n.a.

* Findings during sigmoidoscopy and colonoscopy;
Advanced adenoma: adenoma ≥10 mm, villous component (≥25% villous) or high-grade dysplasia;

and CRC in 14 (0.5%) screenees (Table 2). Of all detected CRCs (n=14) due to FIT screening, 12 (86%) were early stage (Stage I 5; Stage II 7) and two were advanced (Stage III). The PPV of a FIT for finding an advanced neoplasia (53.3%) or a CRC (10.2%) were similar to the PPV of the gFOBT (respectively p=0.42; p=0.93).

FS evaluation was complete in 1386 screenees (91%). Incomplete examination was due to insufficient bowel preparation in 88 (5.8%) subjects and failure to obtain full introduction (>50cm with straightened scope) in 51 (3.4%) subjects. In total 142 (10.2%) screenees were referred for colonoscopy. In total 1243 screenees without polyps (n=817; 59%) or with non-advanced polyps (424; 31%) were discharged. All but one of the positive screenees underwent a complete colonoscopy (99%). In total 103 screenees (7.4%) had an advanced adenoma and 8 (0.6%) a CRC (Table 2), including six early stage CRCs (75%; stage I 6) and two advanced CRCs (stage III 2). One complication occurred within 30 days after FS. A 67-year old screenee presented one week after FS with symptoms of a colovaginal fistula due to a previous diverticulitis. It was considered that air insufflation might have led to symptoms, since no signs of diverticulitis were seen or biopsies had been taken during FS. An uncomplicated sigmoid resection was performed. In total four patients (1.1%) experienced minimal rectal bleeding following polypectomy during colonoscopy without hospitalisation.

Comparison of advanced neoplasia detection rate and yield

Older age (65-75 years: OR 2.3; CI 1.7-3.2) and male sex (OR 2.7; CI 2.0-3.6) were independent predictors for detecting advanced neoplasia. After adjusting for age and sex (Table 3), FIT detected significantly more advanced neoplasia than gFOBT (OR 2.0; CI 1.3-3.2). The DR of advanced neoplasia was considerable higher in the FS arm than in the gFOBT (OR 7.0 CI 4.6-10.7) and FIT (OR 3.4; CI 2.5-4.7) arms. The DR of CRCs did not differ significantly among the three screening arms (Table 3).

The diagnostic yield of advanced neoplasia per 100 invited subjects was significantly higher with FIT (1.5; CI 1.2-1.9) than with gFOBT (0.6; CI 0.4-0.8; p<0.001). FS demonstrated the highest diagnostic yield of advanced neoplasia of 2.4 (CI 2.0-2.8) per 1000 invited subjects compared to gFOBT (p<0.001) and FIT (p<0.001).

Table 3: Odds ratios for the probability of detection of colorectal neoplasia in screened individuals which FIT and FS in comparison with gFOBT.

	Advanced Neoplasia OR (CI)	Colorectal cancer OR (CI)
gFOBT	1	1
FIT	2.0 (1.3-3.2)	1.8 (0.7-4.7)
FS	7.0 (4.6-10.7)	2.2 (0.8-6.3)

Advanced neoplasia: adenoma ≥10 mm, villous component (≥25% villous) or high-grade dysplasia; colorectal cancer.

DISCUSSION

Our data demonstrated a 12% higher participation rate to FIT than gFOBT screening, which is in agreement with the study of van Rossum et al, who used a similar study design.[24] It has been postulated that dietary restrictions required for gFOBT screening are responsible for a lower uptake.[26] However, our study shows that gFOBT screening performed without dietary restrictions remains associated with a lower uptake than FIT screening. A more demanding sampling procedure and the number of consecutive bowel movements that had to be collected (gFOBT three vs. FIT one) seem likely explanations for this difference in participation rate.[27]

Participation to FS screening was significantly lower than to both FOBTs. The participation rate to FS screening in our population is in agreement with most previous population-based FS screening studies [16, 17, 21], but significantly lower than seen in the Norwegian FS screening trial (67%).[21] Our data on participation cannot be directly compared to studies where only eligible and interested respondents to a questionnaire were included in the study.[20, 22] However, multiplying inclusion with participation rates among those included results in overall participation rates in the range of 10-39%.[20, 22] Furthermore, invitees in our study were asked to schedule their own FS appointment, which may have negatively influenced the participation rate. In other studies the appointment for FS was prefixed to be confirmed or modified.[20, 22]

Sex and age were independent predictors for participation in all screening arms. In both FOBT arms, men were less likely to attend. A low participation rate was especially found among men aged 50-55 years (gFOBT 37%; FIT 51%). In contrast, uptake of FS screening was lower among women. This is in accordance with previous studies.[16, 17, 20, 22] Attitude and believes about FS screening might form a barrier to FS screening. Women more often experience fear and embarrassment to undergo FS.[28] A special approach to women in a future nation-wide FS screening programme should therefore be considered.

FS screening detected a substantial higher proportion of advanced neoplasia than both FOBTs, mainly due to a high DR of advanced adenoma (7.4%). This higher proportion of advanced neoplasia detected at FS suggests a more significant CRC incidence and mortality reduction with FS than with FOBT screening. However, the comparison of the DR between both FOBTs and FS screening in this study is limited, since only one screening round was taken into account. Data of successive FOBT screening rounds should be considered to obtain a more accurate comparison of the DR of both FOBTs and FS screening. Our results did demonstrate a respectively three and seven times higher DR of advanced neoplasia of FS compared to FIT and gFOBT screening suggesting a more favourable cumulative DR of advanced neoplasia for a five-yearly FS compared to a biennial gFOBT or FIT screening programme. A 10-yearly interval for FS screening might be justified if an experienced endoscopist performed an examination of at least the distal 50 cm of the colon on well-prepared subjects. These criteria are not routinely achieved in many screening settings. Current guidelines therefore recommend a 5-year

screening interval.[29] Further information on the optimal screening interval is awaited from the ongoing prospective FS studies.[20-23]

The DR of advanced neoplasia (8.0%) in the FS arm was high compared to other studies (3.6-5.2%).[16, 17, 20-22] A possible explanation for the higher DR may lie in inclusion of subjects between 65 and 74 years of age whereas others included subjects between 55 and 64 years of age, since more advanced neoplasia were detected in screenees aged 65-74 than screenees aged 50-64.[20, 22] This is in agreement with studies reporting an increased prevalence of advanced neoplasia at older age.[23, 30, 31] The high DR can also be explained by a more extended endoscopic examination during FS. In this study, FS was performed until the splenic flexure (81% of completed FS) or at least proximal descending colon, while other studies reached for the transition from sigmoid to descending colon as anatomic extent of FS.[20, 22, 23]

A high compliance of positive screenees to a follow-up colonoscopy positively influences the DR. In this study, nearly all positive screenees underwent a colonoscopy (97%). This is significantly higher than observed in other screening studies in which participation rates for colonoscopy after FOBT or FS screening generally ranged between 80-93%.[11, 16, 17, 20] This difference in compliance rate may be population dependent. However, our compliance rates to colonoscopy after a positive gFOBT or FIT were considerably higher than observed in the study of van Rossum et al (83%), which had a similar design and was conducted in the same country.[24] We think that this difference was primarily due to the fact that we, other than van Rossum et al., put the GP in charge of informing the screenee on the positive test result and further handling the referral of the screenee to one of the affiliated hospitals. The GP thus acted as a central stakeholder in the follow-up process.

This study has some limitations. Firstly, the trial has been performed in a screening-naïve population. A previous European study reported a low awareness of CRC and CRC screening in Europe and especially in The Netherlands.[32] Awareness of CRC and the effectiveness of screening does increase participation.[33] Therefore various media were used to promote this study. However, maximizing awareness requires time and effort. We hypothesize that this may further increase the uptake of screening. Secondly, in this study a pre-randomisation design was used to reflect a nation-wide screening programme as closely as possible. Subjects meeting the exclusion criteria were therefore excluded after randomisation. Exclusion numbers were higher in the FS arm than in the other arms partly due to the extra opportunity of recognising exclusion criteria for FS subjects during the telephone call they had to make. Not excluding those subjects would not have changed the participation rates considerably (gFOBT 47.5%, FIT 59.5%, FS 30.4%) and did therefore not influence the results of this study. Thirdly, this study describes the first screening rounds in our population. Data on participation and detection rates of successive screening rounds are needed to provide insight in long-term effectiveness of a population-based screening programme. Fourthly, colonoscopy was not incorporated as a primary screening tool in this study. We acknowledge that colonoscopy is considered the gold standard for CRC screening. However, colonoscopy as primary screening tool is hampered by a

low participation rate and prospective data on the efficacy are lacking. Finally, we only referred screenees for colonoscopy if one of the predefined high risk criteria was met at FS. Screenees with two or fewer tubular adenomas < 10mm were therefore not referred for colonoscopy. Our approach was in agreement with two large ongoing trials studying the impact of first round FS screening on CRC mortality [22, 34], but in contrast with another European RCT on FS.[21] In the latter study, all subjects with a distal adenoma of any size were referred for colonoscopy. Our approach has the disadvantage of missing cases with proximal advanced neoplasia in the presence of no more than two small distal tubular adenomas. However, a previous study reported that 1.9% of these screenees with one or two small distal adenomas (5-9mm) have proximal advanced lesions compared to 9.9% of screenees with distal adenomas $\geq$10 mm.[34] Our referral criteria therefore limit the required colonoscopy capacity while referring screenees with a higher risk on a proximal advanced neoplasia.

In conclusion, this randomised population-based CRC-screening trial demonstrates that FIT outperforms gFOBT screening in participation and detection rate. FIT screening should therefore be strongly preferred over gFOBT screening. Apart from this, it is important to recognise that FS screening in a first screening round provides a considerably higher diagnostic yield of advanced adenomas and CRC per 100 invitees than both FOBTs, despite a lower participation rate. This supports the consideration of a dual-mode screening programme, offering FS as first screening method and FIT as alternative. Long-term prospective RCTs have to be awaited to determine the CRC incidence and mortality reduction due to HT and FS screening.

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Chapter 3

Screening for colorectal cancer; random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels

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ABSTRACT

Immunochemical faecal occult blood testing (FIT) provides quantitative test results, which allows optimisation of the cut-off value for follow-up colonoscopy. We conducted a randomised population-based trial to determine test characteristics of FIT (OC-Sensor micro, Eiken, Japan) screening at different cut-off levels and compare these to guaiac-based faecal occult blood test (gFOBT) screening in an average risk population. A representative sample of the Dutch population (n=10011), aged 50-74 years, was 1:1 randomised before invitation to gFOBT and FIT screening. Colonoscopy was offered to screenees with a positive gFOBT or FIT (cut-off 50ng haemoglobin/ml). When varying the cut-off-level between 50 and 200ng/ml, the positivity rate of FIT ranged between 8.1% (95% CI 7.2-9.1%) and 3.5% (CI 2.9-4.2%), the detection rate of advanced neoplasia ranged between 3.2% (CI 2.6-3.9%) and 2.1% (CI:1.6-2.6%), and the specificity ranged between 95.5% (CI 94.5-96.3%) and 98.8% (CI 98.4-99.0%). At a cut-off value of 75ng/ml the detection rate was two-times higher than with gFOBT screening (gFOBT:1.2%; FIT:2.5%; p<0.001), while the number needed to scope (NNscope) to find one screenee with advanced neoplasia was similar (2.2 vs. 1.9; p=0.69). FIT is considerably more effective than gFOBT screening within the range of tested cut-off values. From our experience, a cut-off value of 75ng/ml provided an adequate positivity rate and an acceptable trade-off between detection rate and NNscope.

INTRODUCTION

Colorectal cancer (CRC) is a major health problem in the Western World. Screening can reduce CRC-related mortality due to detection of early carcinomas and removal of pre-malignant lesions.[1, 2] The American Gastroenterology Association (AGA)[3], the US Multi-Society Task Force [4], Asia Pacific Working Group on Colorectal Cancer screening[5] and the European council recommend CRC screening for average risk individuals over 50 years of age.[6] Several countries have a nation-wide screening programme based on gFOBT, since this is the only available test with a proven mortality reduction [7-9], but consider changing to an immunochemical FOBT (FIT) programme based on accumulating evidence that FIT is superior to gFOBT screening, including a higher attendance [10-12] and detection rate [10, 13, 14], as well as a higher sensitivity without a significant drop in specificity.[13, 15-19] Furthermore, FIT specifically binds human haemoglobin, which makes drugs and diet restrictions superfluous.

Immunochemical faecal occult blood testing samples can be analysed automatically, which has important advantages for reproducibility, quality control, capacity, and thus personnel need and costs.[17, 20] Another advantage of FIT is the quantitative test results, which allows determining an optimal cut-off value for a nation-wide screening programme.[13, 16, 17, 21, 22] The cut-off value for a positive test can be based on a positivity rate that meets the available colonoscopy resources. At the same time, the number of colonoscopies is an important determinant of the neoplasia detection rate, and thus of the potential preventive effect of a CRC screening programme.

Data on positivity rate and test performance at different cut-off levels of FIT screening in an average risk population are highly needed to determine the optimal cut-off value for FIT screening. We therefore conducted a randomised trial to compare the positivity rate, detection rate and specificity of FIT (OC-Sensor micro, Eiken Chemical Co., Tokyo, Japan) screening at different cut-off levels with gFOBT (Hemoccult II; Beckman Coulter Inc., Fullerton, CA, USA) screening in an average risk screening naïve population.

METHODS

Study population

The study was performed in the Rijnmond region in the Southwest of the Netherlands. This region includes Rotterdam and surrounding villages and harbours 338000 inhabitants in the target population. The region thus combines both rural and urban settings. Ten thousand eleven individuals aged 50-74 years old were randomly selected from the Municipal registries. The selected individuals were 1:1 randomised per household after stratifying for age, sex and social economic status into group A (gFOBT) or B (FIT) using a computer generated allocation algorithm (Tenalea, Amsterdam, The Netherlands) (Figure 1). Randomisation occurred before

invitation. Informed consent was asked after randomisation. Individuals with a history of inflammatory bowel disease or CRC, a colonoscopy, sigmoidoscopy or barium contrast enema in the last three years, major health problems or inability to sign informed consent were excluded. Recruitment took place between November 2006 and November 2007.

Interventions

The randomly selected 10011 individuals were sent a pre-invitation letter containing information on CRC screening. Two weeks later an invitation letter was sent with information on possible advantages and risks of screening. This was accompanied by an informed consent form, which had to be signed and returned. A test set was sent along with the invitation. A reminder was sent six weeks afterwards to all non-respondents. Information about the study was further given by direct visits of research physicians to all general practitioners (GP) in the region, as well as via a dedicated website (www.dikkedarmkankerpreventie.nl), mailings and information sites of the municipality offices, regional newspapers, and national and regional broadcasting.

Group A: Guaiac-based FOBT

All individuals randomised to gFOBT received three guaiac imprinted test cards (Hemoccult II) to be used on three consecutive bowel movements without dietary restrictions or medication limitations. Participants returned the test kit by mail to the Gastroenterology and Hepatology laboratory of the Erasmus Medical Centre. Tests were analysed without re-hydration. A test was considered positive if at least one of six panels was positive. A digital picture of test cards was taken and stored in a database. As a quality control, 241 (10%) photographs were re-evaluated by a second technician blinded for the initial test results. A third technician reviewed the photographs in case of inter-observer variation.

Group B: Immunochemical FOBT

Subjects randomised to FIT screening received one FIT kit (OC-Sensor micro) to collect a single faecal sample of one bowel movement without dietary restrictions or medication limitations. Participants returned the test kit by mail to the same laboratory that analysed the gFOBT for quantitative analysis using the automatic OC-Sensor micro instrument (Eiken Chemical Co., Tokyo, Japan). Participants were referred to colonoscopy at haemoglobin levels above 50ng/ml.

Follow-up

In case of a negative gFOBT or FIT, both the general practitioner (GP) and the participant were informed by mail within two weeks. No further follow-up was necessary. In case of a positive gFOBT or FIT (faecal Hb level ≥ 50ng/ml), the GP was informed both by telephone and mail within two weeks. The GP informed the participant about the test result and referred the participant for colonoscopy. A colonoscopy was scheduled within two weeks after the screening test results had become available.

Colonoscopy

All colonoscopies were performed in eight hospitals and performed by experienced endoscopists (individual experience >200 colonoscopies). The reach of the endoscope in cm and the location, as well as the adequacy of bowel preparation was recorded. During colonoscopy, characteristics including size, pedunculated or sessile aspect and location of all polyps were noted and recorded. Location was defined as rectum, sigmoid, descending, transverse, ascending colon or cecum and measured in cm from the anal verge with the endoscope in straightened position. Size of each polyp was estimated using an open biopsy forceps with 7mm span. An experienced gastrointestinal pathologist evaluated all removed polyps. In accordance with the international classification, CRC was defined as the invasion of malignant cells beyond the muscularis mucosa. Patients with intramucosal carcinoma or carcinoma in situ were classified as having high-grade dysplasia.

Ethical approval

The study was approved by the Dutch Ministry of Health (2006/02WBO). The approval included the pre-randomisation design. The study letters and information brochures were approved by the Institutional Review Board of the Erasmus Medical Centre (MEC-2005-264).

Statistical analysis

Differences in proportions between screening strategies were calculated using a χ^2 test. Differences in means between screening strategies were calculated using a Student t-test. All p-values were two-sided and considered significant if <0.05. Uni- and multivariate logistic regression analyses were used to determine the influence of sex and age on positivity rate, number needed to scope, detection rate and number needed to screen. The positivity rate was defined as the proportion of participants having a positive gFOBT or FIT test. For FIT, the positivity rate was separately calculated for cut-off levels of respectively 50, 75, 100, 125, 150, 175 and 200ng/ml. The detection rate was defined as the proportion of participants having advanced neoplasia. This was calculated as the number of screenees with an advanced neoplasia divided by all screenees with a complete screening test. Advanced neoplasia included CRC, and advanced adenoma. Advanced adenoma was defined as adenoma ≥10 mm, or with histology showing either a ≥25% villous component or high-grade dysplasia. We compared faecal haemoglobin measurements between screenees with a normal colonoscopy and screenees with non-neoplastic polyps, non-advanced adenomas, advanced adenomas and CRC as most advanced lesion by the Kruskal–Wallis nonparametric analysis of variance (ANOVA) and the Mann–Whitney test, since the data were not normally distributed. Participation, positivity and detection rate, positive predictive value (PPV) and specificity were calculated and described as percentages with 95% confidence intervals (CI). The specificity for advanced neoplasia and CRC was calculated under the rare disease assumption as the ratio of number of all negative screenees and total number of screenees subtracted by the number of true positives.[23] Number

needed to scope describes the number of colonoscopies to find one screenee with an advanced neoplasia or CRC. Number needed to screen was calculated as the number of complete screening tests needed to find one advanced neoplasia or CRC. Differences in PPV between sexes or age groups in the FIT arm were described for a cut-off of 100ng/ml, since this cut-off value is most commonly used.[10, 16, 21, 24]

RESULTS

In total 10011 subjects were randomised prior to invitation to one of two FOBTs. Three-hundred-seventy (3.7%) were excluded from analyses (332 subjects met one of the exclusion criteria, 26 had moved away and 12 had died). A total of 2375 out of 4796 (50%; CI 48-51%) participants attended gFOBT screening. The gFOBT was analysable in 2351 cases (99%). 2979 out of 4843 (62%; CI 60-63%) subjects attended FIT screening and the test was complete in 2975 subjects (99.9%) (Figure 1). The distribution of age (mean ± SD gFOBT 61±7 yrs; FIT 61±7 yrs old) and sex (male gFOBT 46%; FIT 48%) of the analysable subjects did not differ between the two screening arms.

Proportion of positive tests

In total 65 screenees had a positive gFOBT (2.8%; CI 2.2-3.6%). Immunochemical faecal occult blood testing was positive in 241 screenees (8.1%; CI 7.2-9.1%) at a 50ng/ml cut-off and in 103 screenees (3.5%; CI 2.9-4.2%) at a 200ng/ml cut-off (Table 1). A significant decrease in the proportion of positive tests was seen between a cut-off value of 50 and 75ng/ml (8.1 vs. 5.7%), followed by a more gradual decrease between 75 and 200 ng/ml (Table 1). Male screenees were more likely to have a positive gFOBT (3.7 vs. 1.9% OR 1.4 CI 1.1-1.8) or FIT (FIT^{100}: 6.8 vs. 3.0%; OR 2.3; CI 1.6-3.3) than female screenees. The proportion of positive gFOBTs was slightly higher in screenees aged 60-74 than in screenees aged 50-59 yrs old, but this difference was not significant (3.1 vs. 2.3%; OR 1.3; CI 0.8-2.2). In the FIT arm, the proportion of positive tests was significantly higher in screenees aged 60-74 years than in screenees aged 50-59 years (FIT^{100}: 6.1 vs. 3.3%; OR 1.8; CI 1.3-2.6) (Fig 2).

Colonoscopy findings per test and cut-off value

Sixty-two (95.4%) of the 65 gFOBT-positive screenees and 226 (93.8%) of the 241 screenees with a FIT result ≥50ng/ml underwent a colonoscopy. A double contrast barium enema was performed in three subjects with an incomplete colonoscopy. Two colonoscopies were incomplete due to an obstructing tumour. The colonoscopy findings are shown in Table 2 and are related to the amount of haemoglobin in the faeces. A significantly higher proportion of screenees with faecal haemoglobin levels of 150-200 (48%) and ≥200 (61%) had advanced neoplasia than screenees with faecal haemoglobin levels of 50-150ng (25%) (respectively p=0.009 and

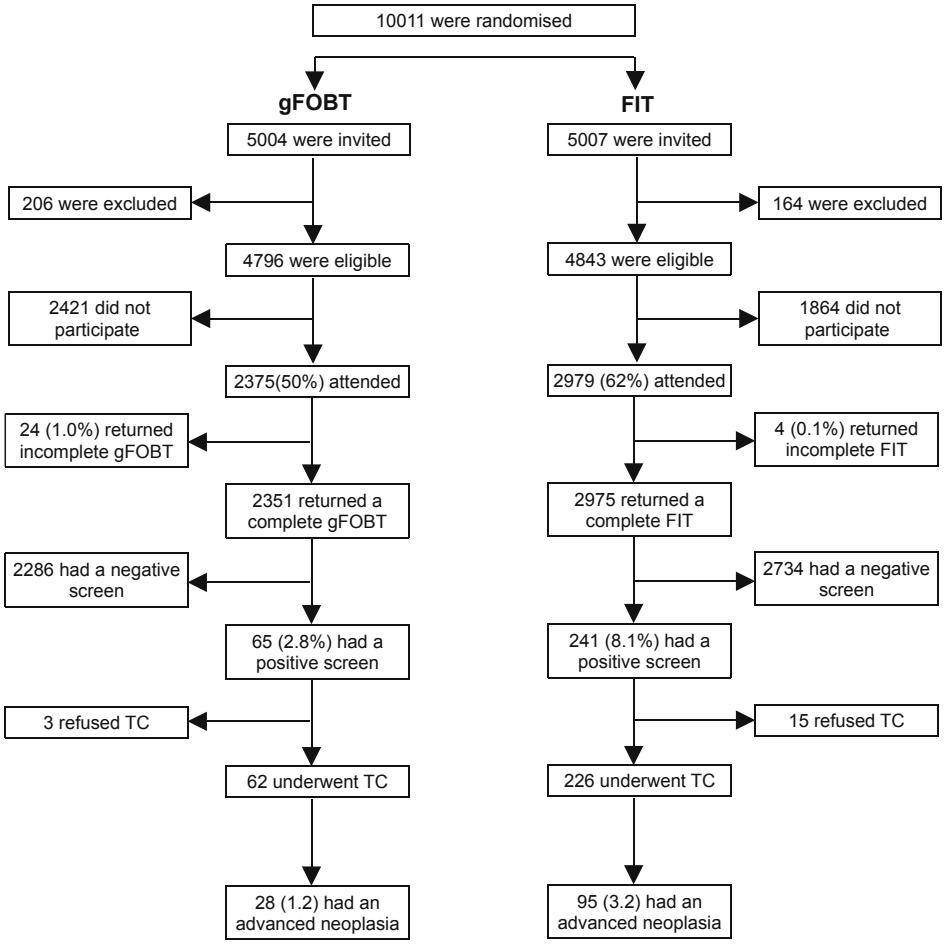

Fig 1: Trial profile.

p<0.001), whereas the proportions were similar amongst screenees with values of 50-100ng/ml and 100-150ng/ml (25 vs.18%; p=0.60)

Haemoglobin levels per finding

The median faecal haemoglobin (Hb) level of positive screenees with a normal colonoscopy was 93 ng/ml. Median Hb measurement in screenees with as most advanced finding a non-neoplastic polyp was 109 ng/ml, a non-advanced adenoma was 112 ng/ml, an advanced adenoma was 373 ng/ml, a CRC was 404 ng/ml. Faecal Hb levels of screenees with a normal colonoscopy did not significantly differ from those of screenees with non-neoplastic (p=0.88) or non-advanced adenoma (p=0.89), while the faecal Hb level of screenees with an advanced adenoma or CRC were significantly higher than those of screenees with a normal colonoscopy

Table 1: Test characteristics of gFOBT and FIT at different cut-off levels.

	Cut-off	Positivity rate	PPV		NNscope		Specificity		Detection rate				NNscreen	
	ng/ml	n	% (CI)	Adv neoplasia % (CI)	CRC % (CI)	Adv neoplasia n	CRC n	Adv neoplasia % (CI)	CRC % (CI)	Adv neoplasia n	Adv neoplasia % (CI)	CRC n	CRC % (CI)	Adv neoplasia n	CRC n
gFOBT		65	2.8 (2.2 - 3.6)**	45 (33-58)	10 (4 - 20)	2.2	10.3	98.5 (97.9-99.0)	97.6 (94.8-98.9)*	28	1.2 (0.8-1.7)	6	0.3 (0.1 - 0.6)	84	392
FIT	50	241	8.1 (7.2 - 9.1)*	42 (36-49)	7 (4 - 11)	2.4	14.1	95.5 (94.5-96.3)*	92.9 (88.8-95.5)*	95	3.2 (2.6-3.9)*	16	0.5 (0.3 - 0.9)	31*	186
	75	170	5.7 (4.9 - 6.6)*	49 (42-57)	9 (5 - 14)	2.0	11.6	97.2 (96.5-97.7)*	95.0 (91.8-97.0)*	80	2.7 (2.2-3.3)*	14	0.5 (0.3 - 0.9)	37*	213
	100	143	4.8 (4.1 - 5.6)*	53 (45-61)	10 (6 - 17)	1.9	9.8	97.8 (97.2-98.2)*	95.8 (93.2-97.5)*	73	2.5 (2.0-3.1)*	14	0.5 (0.3 - 0.8)	41*	213
	125	128	4.1 (3.4 - 4.9)*	57 (48-65)	11 (6 - 17)	1.8	9.5	98.2 (97.7-98.6)	96.3 (93.8-97.8)*	70	2.3 (1.9-3.0)*	13	0.4 (0.3 - 0.8)	43*	229
	150	120	4.0 (3.4 - 4.8)*	60 (51-69)	11 (7 - 19)	1.7	8.8	98.4 (98.0-98.7)	96.6 (94.2-98.0)*	69	2.3 (2.8-2.9)*	13	0.4 (0.3 - 0.8)	43*	229
	175	107	3.6 (3.0 - 4.3)*	63 (53-72)*	12 (7 - 20)	1.6*	8.5	98.7 (98.3-99.0)	97.0 (95.0-98.3)*	64	2.2 (1.7-2.7)*	12	0.4 (0.3 - 0.8)	46*	248
	200	103	3.5 (2.9 - 4.2)*	62 (52-71)*	12 (7 - 20)	1.6*	8.2	98.8 (98.4-99.0)	97.1 (95.0-98.4)*	61	2.1 (1.6-2.6)*	12	0.4 (0.3 - 0.8)	49*	248

*p<0.05 compared to gFOBT; Advanced neoplasia: adenoma ≥ 10 mm, villous component (≥ 25% villous) or high-grade dysplasia; CRC.

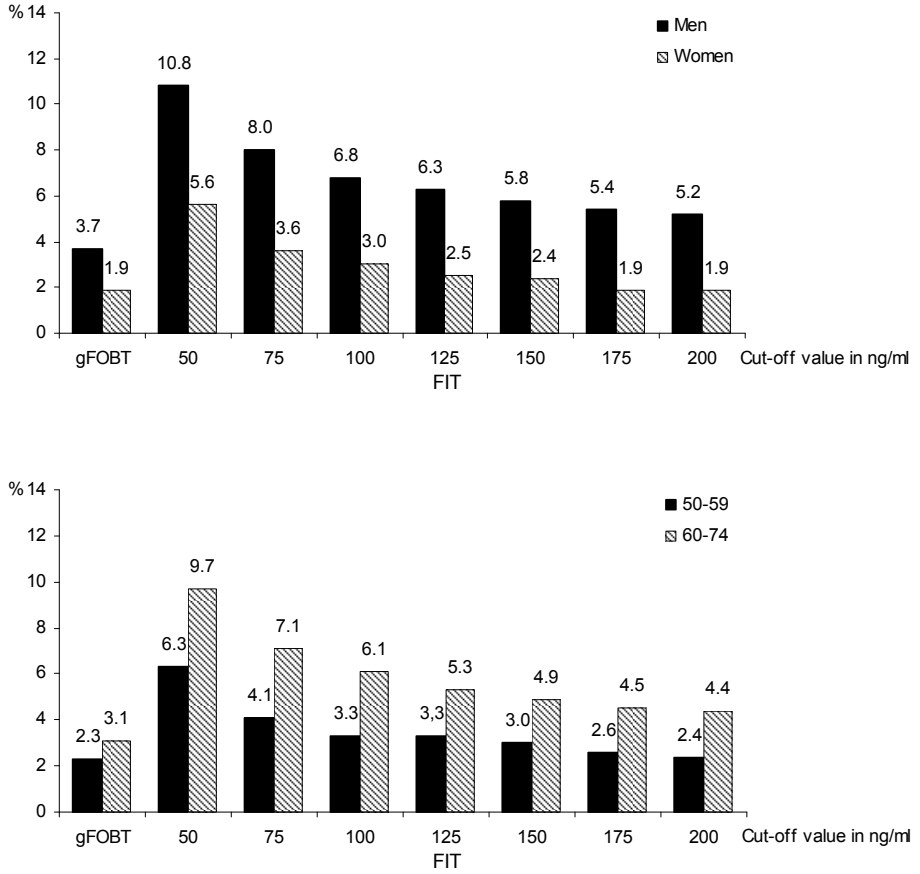

Fig 2: Positivity rate of gFOBT and FIT at different cut-offs in men and women aged 50-59 and 60-74 years old.

Table 2: Colonoscopic findings per screenee according to the haemoglobin levels of the positive FIT.

	Haemoglobin level in ng/ml			
	50-100 n (%)	100-150 n (%)	150-200 n (%)	≥200 n (%)
Total screenees	89 (100)	22 (100)	17 (100)	98 (100)
No findings	37 (42)	11 (50)	4 (23)	19 (19)
Non-neoplastic polyp	8 (9)	1 (5)	3 (18)	3 (3)
Non-advanced adenomas	22 (25)	6 (27)	2 (12)	15 (15)
Advanced adenomas	20 (22)	3 (14)	7 (41)	49 (49)
CRC	2 (2)	1 (5)	1 (6)	12 (12)
Advanced neoplasia	22 (25)	4 (18)	8 (47)	61 (61)

Advanced adenoma: adenoma ≥ 10 mm, villous component (≥ 25% villous) or high-grade dysplasia; CRC: colorectal cancer.

(both p<0.001). The difference between those with advanced adenoma and those with CRC was not significant (p=0.53).

Test characteristics

The positive predictive value (PPV) of gFOBT for advanced neoplasia and for CRC was 45% (CI: 33-58%) and 10% (CI: 4-20%) respectively. Immunochemical faecal occult blood testing demonstrated a more favourable PPV for detecting advanced neoplasia at higher cut-off values (Table 1), but this difference was only significant at cut-off values >175ng/ml (gFOBT 45% vs. FIT^{175} 63%; p=0.029 and FIT^{200} 62%; p=0.035). The PPV for CRC was similar for gFOBT and FIT at all cut-off levels, although the PPV of FIT steadily increased with increasing cut-off value (Table 1).

The NNscope to detect one screenee with an advanced neoplasia or CRC was respectively 2.2 and 10.3 for gFOBT. The corresponding numbers with FIT screening were 2.4 and 14.1 at 50ng/ml and 1.6 and 8.2 at 200ng/ml cut-off values (Table 1) for advanced neoplasia and CRC respectively. Men demonstrated a lower NNscope for advanced neoplasia than women (gFOBT: men 1.8; women 3.8; p=0.04; FIT^{100}: men 1.7; women: 2.5; p=0.03) (Fig 3). No differences in NNscope for advanced neoplasia or CRC were seen between different age groups (gFOBT p=0.33; FIT^{100} p=0.81).

The estimated specificity for not having advanced neoplasia and CRC was significantly lower for FIT at cut-off values ≤100ng/ml than gFOBT (Table 1). Above a cut-off value of 100ng/ml the estimated specificity was similar to the gFOBT.

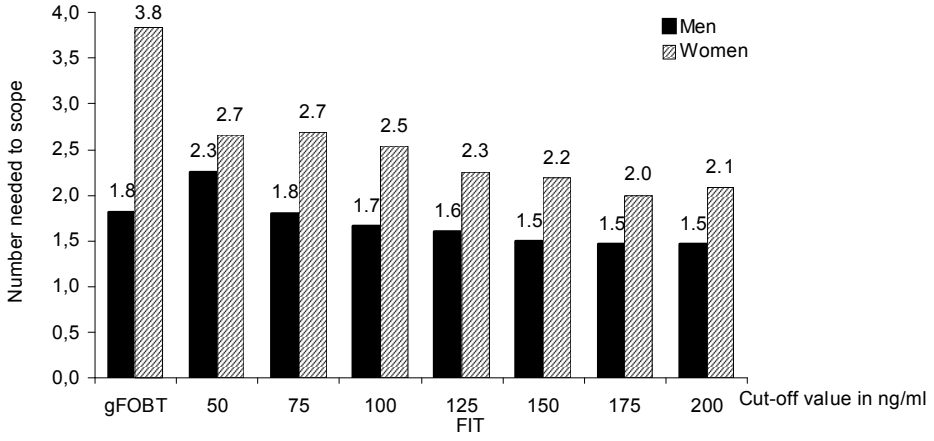

Fig 3: Numbers needed to scope to find one screenee with an advanced neoplasia in men and women at different cut-off values.

Detection rate

In the range of tested cut-off levels, FIT detected more advanced neoplasia than gFOBT (gFOBT: 1.2%; 95% CI 0.8-1.7%; FIT^{50}: 3.2%: CI 2.6-3.9%; FIT^{200}: 2.1%; CI 1.6-2.6%), while similar detection rates for CRC were found for gFOBT and FIT screening.

Male sex was associated with a higher detection rate of advanced neoplasia in both screening arms (gFOBT: OR 4.2; CI 1.7-10.4; FIT^{100}: OR 3.5 CI 2.0-6.1). Screenees aged 60-74 years old demonstrated a higher detection rate of advanced neoplasia than screenees aged 50-59 years old in the FIT arm (FIT^{100} OR 1.9; CI 1.2-3.2), while no significant difference between both age groups was found in the gFOBT arm (OR 1.5; CI 0.7-3.3).

The number needed to screen (NNscreen) to find at least one advanced neoplasia was favourable at all cut-off levels for FIT compared to the gFOBT arm (Table 1). Male screenees demonstrated significantly lower numbers needed to screen to detect one advanced neoplasia than women (gFOBT: men 57 vs. women 181; p=0.002; FIT 100^{100}: men 26 vs. women 91; p<0.001).

DISCUSSION

We compared FIT screening at different cut-off levels with conventional guaiac-based FOBT screening in an average risk screening-naïve population. Our results demonstrate that FIT within the complete range of tested cut-off values (50-200ng/ml) outperforms gFOBT screening as it is associated with both higher attendance as well as higher detection rates of advanced neoplasia, even though the positive predictive value for detecting advanced neoplasia did not differ significantly between both tests. The outperformance of FIT over gFOBT on both attendance and yield is very relevant for the potential impact of faecal occult blood-based screening on the mortality due to colorectal cancer.

Furthermore, FIT provides quantitative results, which allows determination of an optimal cut-off value for a nation-wide screening programme based on colonoscopy capacity and the intended detection rate in the screened population. A low cut-off value (50ng/ml) provided a high detection rate of advanced neoplasia, but also more false positive test results and thus a higher number of unnecessary colonoscopies. False-positive results are associated with anxiety [25] and increased costs.[26] Increasing the cut-off value resulted in a decrease in detection rate but a more favourable positive predictive value. The key question is at which cut-off value the magnitude of benefits (possible early detection of CRC or removal of adenomas) is sufficient to outweigh the harms (burden, complications, demand on colonoscopy capacity, and costs of screening). The cut-off at which this trade-off becomes acceptable must be determined in a full cost-effectiveness analysis. However, the ratio between detection rate and number needed to scope to find one screenee with an advanced neoplasia is a good indicator for this trade-off, since it reflects both benefit (detecting an advanced neoplasia) and harm (the need to undergo colonoscopy). We found that the NNscope was higher with FIT than with gFOBT screening when using a FIT cut-off of 50 ng/ml, but this changed in favour of FIT when increasing the cut-off to 75 ng/ml (Table 1). At a 75ng/ml cut-off value, the detection rate with FIT was two-fold higher than with gFOBT. At the same time, increasing the FIT cut-off from 50 to 75 ng/ml

had a considerably stronger limiting effect on the proportion of FIT positives (falling from 8.1 to 5.7%) than any other similar further increase of the FIT cut-off (Table 1). Further increasing the cut-off level from 75 to 100ng/ml would result in a larger decline in detection rate (8.8%) than in number needed to scope (7.3%) and therefore a less favourable trade-off (Table 1). For these reasons, we conclude that FIT provided the most optimal trade-of when using a 75ng/ml cut-off value. This conclusion is in agreement with observations from a colonoscopy study determining the one time sensitivity and specificity of the same OC-Sensor micro FIT test in a population of individuals at higher risk for CRC.[17] The latter study and our results come to a lower cut-off than the recommended cut-off value of 100ng/ml by the manufacturer (Eiken Chemical Co., Tokyo, Japan) and by a previous study examining the performance of the OC-Sensor micro at different cut-off levels.[27]

Our findings on positivity rate, positive predictive value (PPV) and the detection rate of CRC at a cut-off of 100 ng/ml are in agreement with other studies using the OC-Sensor micro with this specific cut-off.[10, 21, 27-29] Both our study and the similarly designed study by Van Rossum et al. however found a significantly higher PPV and detection rate for advanced neoplasia (PPV 52-53%, DR 2.4-2.5%) than other studies (PPV 20-39%; DR 0.8-1.2%), even though these studies all focused on the same age group, and applied the same test and definition of advanced neoplasia.[21, 27-29] A possible explanation is that both Dutch studies were carried out in a screening-naïve population, while other studies from Italy and France were performed parallel to a nation-wide programme and therefore were more likely to have included previously screened subjects with a lower risk on advanced neoplasia.[21, 27-29]

The positivity rate is the main driver for the number of colonoscopies among attendants. In countries with a gFOBT screening programme, changing to FIT screening with a 50 ng/ml cut-off value would require a considerable (gFOBT 2.8% vs. FIT$^{50ng/ml}$ 8.1% positivity rate) increase in colonoscopy capacity for screening. This effect is augmented by a higher attendance rate to FIT than to gFOBT screening.[10, 30] Thus, FIT screening enables more efficient screening with increased participation [10, 11, 30] and improved test performances [10, 13, 14, 18, 19, 31, 32], potentially allowing a decrease in screening intensity by lengthening screening interval.

The detection rate of advanced neoplasia was significantly higher in men than in women in both screening arms. Likewise, the number needed to screen to detect an advanced neoplasia was lower in men than in women. Similar differences in detection rates for advanced neoplasia between both sexes were found in two colonoscopy screening studies.[33-35] Furthermore, the CRC incidence rates are on average 1.5 times higher in men than in women aged 50-75 year.[2, 36] Thus, higher pre-test probabilities for advanced neoplasia in men explains this difference. Several studies have therefore suggested to develop sex-specific recommendations for CRC screening.[37, 38] However, these recommendations have so far not been incorporated in CRC screening guidelines, among others because more complex guidelines can negatively influence attendance rate. However, a differentiated approach taking sex and potentially age into account would be relatively easy with FIT screening. One could argue to use different cut-off

values for men and women to achieve a similar number needed to scope, which would result in a considerable higher cut-off value for women than for men (Figure 3).

This study was not designed to estimate the sensitivity and specificity of the faecal occult blood test, since negative screenees did not undergo a colonoscopy (golden standard). The aim of this study was to compare test characteristics of the gFOBT and FIT at different cut-off values. The detection rate and false-positive test results could be used as an indication for respectively test sensitivity and specificity, since both tests were performed in a similar population. Specificity for advanced neoplasia of gFOBT and FIT were estimated under the rare disease assumption based on the number of false positive screenees. The specificity can be overestimated if the number of false negatives increases, which is seen in diseases with a high prevalence and more sensitive tests.[23] Therefore, the specificity of advanced adenoma could be slightly overestimated in both screening arms due to a higher prevalence. Another limitation of the design of this study is that the mean haemoglobin levels per lesion (non-neoplastic polyp, non-advanced adenoma, advanced adenoma or CRC) only pertain to screenees who had a positive test (faecal Hb level ≥ 50ng/ml) and subsequently underwent a follow-up colonoscopy. These results can therefore not be generalised to all screenees. However, this observation could be used for prioritizing of colonoscopies in subjects with a positive test, a topic which can be very relevant in areas and at time periods of shortage of endoscopic capacity, even when all subjects with a test result above a chosen cut-off should undergo endoscopy within a limited time span. Furthermore, this study describes the first screening round in our population. Data on PPV and detection rate of successive screening rounds are needed to provide insight in long-term effectiveness of a population-based screening programme.

In conclusion, this randomised population-based trial provides important data on the test characteristics of FIT screening at different cut-off values. Immunochemical faecal occult blood testing is considerably more effective than gFOBT within the complete range of tested cut-off values. From our experience, a cut-off value of 75ng/ml provided an adequate positivity rate and an acceptable trade-off between detection rate and number needed to scope to find a screenee with an advanced neoplasia. Increasing the cut-off value can be considered in case of insufficient colonoscopy capacity, at the cost of a gradual decrease in detection rate. The optimal cut-off value within a specific population can be based on a local screening programme taking major determinants into account including the incidence of neoplasia, the intended screenings-interval, colonoscopy capacity, and cost-efficacy. With this in mind, the use of variable cut-offs for different sub-groups is a further option for individualised CRC screening.

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Chapter 4

Uptake of faecal immunochemical test screening among non-participants in a flexible sigmoidoscopy screening programme.

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ABSTRACT

A screening programme based on single modality testing may prevent individuals with a preference for a different test from participating. We conducted a population-based trial in a screening naïve population to determine whether non-participants to flexible sigmoidoscopy (FS) screening were willing to attend faecal immunochemical test (FIT) screening. In total 8407 subjects were invited in a primary FS screening programme. Invitees did not know at the time of the primary FS invitation that non-participants would be offered FIT screening. 4407 non-participants of FS screening were invited for a one-sample FIT screening (cut-off 50ng haemoglobin/ml). The participation rate to the primary FS screening program was 31% (CI 30-32%). Among the FS non-participants 25% (CI 24-26%) did attend FIT screening. The overall participation rate of the two-stage recruitment for FS and FIT screening was 45% (CI 44-46%). FIT screenees were older (p=0.02), more often women (p<0.001) and had a lower social economic status (p=0.01) than FS screenees. The detection rate for advanced adenoma was 3.5% (CI 2.5-4.8%), and for CRC 0.3% (CI 0.1-0.8%) among participants to secondary FIT screening. The detection rate of the two-stage recruitment was 202 (6.1%) for an advanced adenoma, and 16 (0.5%) for a CRC. Offering FIT screening to non-participants in a FS screening programme increases the overall participation rate considerably, as a quarter of non-participants of FS screening were willing to attend FIT screening. The attendance remains however lower than for primary FIT screening (62%). Women in the target population were more likely to refuse FS than FIT screening. Countries introducing FS screening should be aware of these preferences.

INTRODUCTION

Compelling evidence supports the effectiveness of screening for colorectal cancer (CRC).[1-5] International guidelines therefore recommend screening for average risk individuals over age 50 years to detect and prevent CRC.[6-8] There are various test methods available for CRC screening. Each test has been shown to be cost-effective and some even cost-saving, but tests differ in the level of supporting evidence, reducing effect on CRC related mortality, potential risk and test burden.[9, 10] The faecal occult blood test (FOBT) derives its reducing effect on CRC mortality from early detection of CRC.[1] Endoscopic screening strategies like flexible sigmoidoscopy (FS) and total colonoscopy (TC) have been proven to be effective at both early detection of CRC and removal of pre-malignant lesions (adenoma).[2-5, 11] Endoscopic screening therefore provides a potential larger effect on CRC related mortality than FOBT screening. Irrespective of the method chosen, screening programmes have to be widely accepted to be effective on a population level. A possible drawback for the implementation of an endoscopic based nationwide screening programme is the reported low participation rate.[12-18] In the Netherlands were FOBT and FS have been considered as mass screening tool in a randomised trial, uptake of FS was significantly lower than of FOBT screening (32 vs. 62%).[13] A significant proportion of the population would therefore not receive any screening if a single test population-based screening programme based on FS would be introduced.

Offering a non-invasive test to non-participants of a FS screening strategy may increase the overall uptake of CRC screening in a population, as some non-participants may have a clear preference for another screening test. Several studies demonstrated that a preference for FOBT was based on the simple and non-invasive character of the test, whereas FS was preferred based on test accuracy.[19-22] A screening programme based on a single test may prevent individuals with a specific preference for a different test from participating. It is however unknown to what proportion of the population this concerns to.

To maximise acceptance of FS screening, it is important to determine reasons for non-participation. Worries about pain, discomfort, or injury associated with FS screening as the main reasons for refusing FS screening.[23] Those barriers may be overcome by offering non-participants an alternative screening test, for example FOBT. However, studies on non-participation almost invariably rely on questionnaires or interviews, are limited by low response rates, and for this reason does not provide adequate insight in the actual decision subjects would make. Therefore data on uptake of FOBT screening among non-participants of a FS based programme are required, as available studies generally considered a single test in one setting.

We conducted a population-based trial to determine uptake and diagnostic yield of faecal immunochemical test (FIT) screening among non-participants of FS screening in an average risk screening naïve population. We compared the overall participation rate with the figures of primary FIT screening. Furthermore, the detection rate of advanced neoplasia of FIT screening

was assessed. This approach allowed insight in reasons for non-compliance to FS screening and to which extend the uptake of a nation-wide screening programme could be increased.

METHODS

As part of a Dutch population based randomised screening trial comparing participation and detection rate of guaiac based faecal occult blood testing (gFOBT), FIT, and FS screening [13], we evaluated the additional uptake and diagnostic yield of FIT screening among non-participants of a FS screening programme. The trial protocol and data on participation rate and diagnostic yield of gFOBT, FIT and FS screening have been described elsewhere.[13] Briefly, a random sample of 15011 individuals was taken by a computer generated algorithm and 1:1:1 randomised using this computer generated algorithm (Tenalea, Amsterdam, the Netherlands). Randomisation was done per postal address after stratifying by age, sex and social economic status (SES) into group A (gFOBT), B (FIT) or C (FS). Randomisation occurred prior to invitation. In total 5000 subjects were invited for FS as part of the randomised trial. The results on uptake and diagnostic yield have been published recently.[13] As a continuation of the study, an additional 3407 subjects were invited for FS using the exact same protocol. Data of all invitees to FS screening will be described in the results section. The data of the invitees directly allocated to FIT are described previously, but will also be included in Table 2 to allow direct comparison of the randomised data.

The SES was based on the data of Statistics Netherlands (www.cbs.nl) providing average SES per postal code area (very high, high, intermediate, low, very low) each representing small neighbourhoods. Individuals with a history of inflammatory bowel disease or CRC, a colonoscopy, sigmoidoscopy or barium contrast enema in the last three years, major health problems, or those who moved away or died were excluded from analyses. Recruitment took place between November 2006 and May 2008. The Dutch Ministry of Health approved the study protocol (2006/02WBO). The study letters and information brochures were approved by the Institutional Review Board of the Erasmus Medical Centre (MEC-2005-264).

Interventions

Details of the recruitment process are described elsewhere.[13] Briefly, all individuals were sent a pre-invitation letter, followed by an invitation letter two weeks later. A test set was sent along with the invitation in case of FIT screening. The FS group received an invitation letter with a telephone number of the screening unit to schedule an appointment. A reminder was sent six weeks afterwards to all non-respondents. At the time of the primary FS invitation subjects were not informed that non-participants would have another test offered. Non-participants to FS screening were invited for FIT screening. The invitation letter, information and test set were similar as used for subjects directly invited for FIT. Information about the study was further

given to all general practitioners (GP) in the region by direct visits of research physicians prior to start of the study, providing them with background information, a contact address, and an information folder. All information was also made available via a dedicated website (www.dikkedarmkankerpreventie.nl), mailings and information sites of the municipality offices, regional newspapers and national and regional broadcasting.

Faecal immunochemical test

Subjects received one FIT kit (OC-Sensor micro, Eiken Chemical Co., Tokyo, Japan) to collect a single faecal sample of one bowel movement. Participants returned the test kit by mail to the laboratory of the Gastroenterology and Hepatology department of the Erasmus University Medical Centre for quantitative analysis using the automatic OC-sensor micro instrument (Eiken Chemical Co., Tokyo, Japan). The test was considered positive above a cut-off value of 50 nanogram haemoglobin/ml.

Flexible sigmoidoscopy

Individuals randomised to FS, once scheduled for an appointment, received a 120ml phosphate enema (Clyssie, B. Braun Medical B.V., Oss, The Netherlands) by mail with instructions for self-administration. Administration of the enema by a nurse in the screening unit was offered as an alternative. Flexible sigmoidoscopy was performed with a regular forward-looking video-colonoscope (Olympus Europe, Hamburg, Germany). All sigmoidoscopies were performed by experienced endoscopists (>200 colonoscopies) in a dedicated screening centre. The endoscope was advanced as far as could be achieved without causing undue pain or distress aiming to reach the splenic flexure. The FS was considered complete when the endoscope was advanced beyond the colon descending–sigmoid junction into the proximal descending colon and more than 50 cm of the anal verge with endoscope in straightened position. Participants did not receive sedatives. All polyps up to a diameter of 9 mm were removed at FS and sent for histological evaluation. Polyps with a diameter of ≥10 mm were left in situ for removal during colonoscopy. Participants were referred for a total colonoscopy (TC) when one of the following criteria was met: presence of a polyp with a diameter ≥10 mm; an adenoma with serrated, villous histology (≥25% villous) or high-grade dysplasia; ≥3 adenomas; ≥20 hyperplastic polyps; or invasive CRC. In accordance with the international classification, CRC was defined as the invasion of malignant cells beyond the muscularis mucosa.

Test results

In case of a positive FS or FIT the GP was informed by telephone and mail within two weeks. The GP informed the participant about the test result and referred the participant for colonoscopy. A colonoscopy was scheduled within four weeks after the screening test results had become available. Participants with a negative FS or FIT were informed by mail within two weeks.

Statistical analysis

Differences in proportions were calculated using the χ^2 test. Differences in means were calculated using a Student t-test. The participation rate per screening test was calculated by dividing participants by all eligible subjects (defined as invited subjects minus the excluded subjects). The overall participation rate was calculated by eligible subjects divided by the total number of participants of FS and FIT screening. Separate uni- and multivariate models were used with participation as function of age, sex, and SES. Interaction of age and sex was determined using a multivariate model. No significant interaction between age and sex was determined (p=0.13). The detection rate was defined as the proportion of screenees with advanced adenoma or CRC. Advanced adenoma was defined as adenoma ≥10 mm, with a villous histology (≥25% villous) or with high-grade dysplasia. The detection rate was calculated using the most advanced lesion detected per screenee. Number needed to screen was defined as number of advanced adenoma or CRC divided by number of participants with a complete screening test. Number needed to invite was defined as number of advanced adenoma or CRC divided by number of eligible screenees. All p-values were two-sided and considered significant if <0.05.

RESULTS

Uptake

First invitation: FS: A total of 8407 subjects were pre-randomised to FS screening and received an invitation. In total 524 subjects met one of the exclusion criteria, leaving 7883 potential participants. Participation rate to the FS program after the first invitation was 26% (CI 25-27%), and increased to 31% (2433/7883; CI 30-32%) after a reminder was sent six weeks later. The mean age of FS screenees was 60.5±SD 6.4, 53% (1279/2433) were men, 23% had a very high, 23% high, 18% intermediate, 18% low, 18% very low SES.

Second invitation: FIT: In total 5450/7883 did not participate of whom 977 reported not wanting to have further invitations for CRC screening for various reasons (e.g. had cancer with or without treatment, were hospitalised for other disease, or mentally disabled) and were therefore not included in this study. The remaining 4473 non-participants of FS screening were invited for FIT screening (Fig 1), of which 66 were excluded from analysis (1.5%; 39 subjects met one of the exclusion criteria, 17 had moved away and 10 had died). The participation rate to FIT screening was 25% (1092/4407; CI 24-26%) (Fig 1). The mean age of screenees was 61.3±SD 6.0, 43% (473/1092) were men, 22% had a very high, 19% high, 19% intermediate, 18% low, 22% very low SES.

Women (28% CI 26-30%) were more likely to attend FIT screening than men (21% CI 19-23%). Uptake was associated with age, as screenees aged 60-64 (28% CI 25-30%; p=0.002) and 65-69 (26% CI 23-30 p=0.035) were more likely to attend FIT screening than screenees aged 50-54

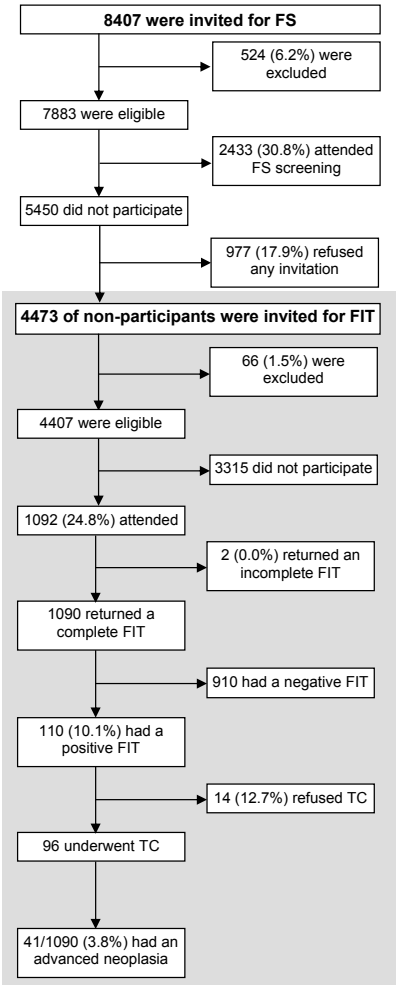

Fig 1: trial profile. The current trial is shown in the grey box.

(22% CI 19-24%). Uptake among screenees aged 55-59 (24% CI 22-26%; p=0.45) and 70-74 (23% CI 20-27%;p=0.20) was similar to screenees aged 50-54. SES did not affect uptake. Multivariate analysis confirmed the univariate results (Table 1).

Two-stage recruitment: The overall participation rate of the two-stage recruitment for FS and FIT screening was 45% ((2433+1092)/(7883-66)) (CI 44-46). The group non-participants to FS screening that did attend FIT screening, were older (61.3 vs. 60.5 yr; p=0.02), more often women (57% vs. 47%; p<0.001) and had a lower SES (p=0.01) compared to the group of subjects that primarily attended FS screening.

Table 1: Uptake of FIT among non-participants to FS screening by age and gender

		N (%)	OR (CI)‡
Men		472/2221 (21)	1
Women		620/2186 (28)	1.5 (1.3-1.7)*
Age groups (years)	50-54	226/1031 (22)	1
	55-59	296/1223 (24)	1.2 (1.0-1.4)
	60-64	275/983 (28)	1.4 (1.2-1.7)*
	65-69	178/675 (26)	1.3 (1.0-1.6)*
	70-74	117/495 (24)	1.1 (0.9-1.4)

* p-value <0.05; ‡ multivariate analysis

Test characteristics

First invitation: FS: FS evaluation was complete in 2231/2433 screenees (92%). Incomplete examination was due to insufficient bowel preparation in 130 (5.3%) subjects and failure to obtain full introduction (>50cm with straightened scope) in 72 (3.0%) subjects. In total 232 (10.4%) screenees were referred for colonoscopy. All but two of the positive screenees underwent a colonoscopy (99%). The most advanced lesion was a non-advanced adenoma in 287 (12.9%; 11.5-14.3%) screenees, these subjects were therefore not referred for a TC. An advanced adenoma was found in 164 (7.4%; CI 6.3-8.5%) screenees and a CRC in 13 (0.6%; 0.3-1.0%) screenees (Table 2). The number needed to screen to detect an advanced adenoma was 14 (CI 12-16) and for a CRC was 172 (CI 100-295). Forty-eight (CI 41-56) screenees had to be invited to detect one advanced adenoma and 606 (CI 352-1044) to detect a CRC.

Second invitation: FIT: The FIT was incomplete in 2/1092 (0.2%) of the participants. In total 110/1090 (10.1%) screenees had a positive test and were referred to undergo a colonoscopy. Fourteen (12.7%) screenees refused to undergo a colonoscopy. Four of the 96 colonoscopies were incomplete and therefore a double contrast barium enema was performed in one screenee and a CT-colonography in two screenees. One screenee had an incomplete examination due to extensive diverticulosis an no further investigation was performed. The most advanced lesion was a non-advanced adenoma in 28 screenees (2.6%; 3.7-1.8%), advanced adenoma in 38 (3.5%; CI 2.5-4.8%) screenees and a CRC in 3 (0.3%; CI 0.1-0.8%) screenees. Stage II CRC was found in two cases. Advanced CRC was found in one screenee (stage IV) (Table 2). The positive predictive value to find an advanced adenoma or CRC was respectively 39.6% and 3.1%. The number needed to screen to detect an advanced adenoma was 29 (CI 21-39) and for a CRC 363 (CI 118-1126). One hundred and six (CI 85-159) screenees had to be invited to detect one advanced adenoma and 1469 (CI 474-4554) to detect a CRC.

Two-stage recruitment: The detection rate with either FS or FIT screening for a non-advanced adenoma was 315 (9.5%; 8.5-10.5%), 202 (6.1%; CI 5.3-6.9%) for an advanced adenoma, and 16 (0.5%; CI 0.3-0.8%) for a CRC. The number needed to screen to detect an advanced adenoma

Table 2: Most advanced lesion and number of adenomas identified by FS screening and FIT screening among non-participants to FS screening.

	Directly allocated to FIT	First-stage: FS screening	Second-stage: FIT screening	Two-stage recruitment
		N (%)	N (%)	N (%)
Participation rate	2979 (62)	2433 (32%)	1092 (25)	3525 (45)
Positivity rate	241 (8.1)	232 (10.4)	110 (10.1)	
Hyperplastic polyp	15 (0.5)	455 (20.4)	4 (0.4)	459 (13.8)
Tubular adenoma <10mm	45 (1.5)	287 (12.9)	28 (2.6)	315 (9.5)
≥10mm	31 (1.0)	78 (3.5)	16 (1.5)	94 (2.8)
Villous histology / HGD	48 (1.6)	86 (3.9)	22 (2.0)	108 (3.3)
Advanced adenoma	79 (2.7)	164 (7.4)	38 (3.5)	202 (6.1)
Carcinoma	16 (0.5)	13 (0.6)	3 (0.3)	16 (0.5)
Number of adenomas				
1	67 (2.3)	303 (13.6)	29 (2.7)	332 (10.0)
2	28 (0.9)	75 (3.4)	17 (1.6)	92 (2.8)
≥3	33 (1.1)	76 (3.4)	22 (2.0)	98 (3.0)

was 16 (CI 14-19) and a CRC was 208 (CI 127-339), and the number needed to invite to detect an advanced adenoma was 39 (CI 34-44) and for a CRC was 489 (CI 300-797).

DISCUSSION

This study determined uptake of FIT screening among non-participants in a population-based FS screening programme. Previous studies have shown major differences in uptake of different screening tests, a difference which has a major impact on the eventual efficacy of population-based screening. This difference is in part related to the expected burden of a test. A recent Italian study found that 23% of non-participants of a FS screening programme reported anticipated pain, discomfort, or injury as main reasons for refusing FS screening.[23] Our results validate this finding in a true experimental setting, since 25% of non-participants to FS screening were willing to undergo a non-invasive and less burdensome FIT test.

Individuals in the target population demonstrate distinct preferences for a screening test, and may persist in their choice over time.[19-22] Screening based on individual preferences for a screening strategy may thus significantly increase uptake. Although this study was not designed to determine uptake when subjects were offered a direct choice, given the two stage method of recruitment, we did find a significant increase in overall participation rate when FIT screening was added to a FS screening programme. Our data demonstrated that participation rate of the group directly allocated to FS screening was 31%.[13] The overall participation rate increased to 45%, which significantly improved the diagnostic yield of the screening programme, as demonstrated by the lower number of invitees to detect an advanced adenoma or CRC. On the other hand, the overall participation rate was considerably lower than we reported in the group directly assigned to FIT screening (62%) (Table 2).[13] The two-stage recruitment used in this trial

can however not be used for a nation-wide programme, as invitees to FS screening were not informed that not participants would be invited for FIT screening. Participants to FS screening, who would have preferred FIT screening if offered a direct choice will feel misinformed. In a nation-wide screening programme invitees should be offered a direct choice.

Two population-based studies in which subjects were offered a direct choice between FOBT and FS screening reported similar uptake rates as obtained with an invitation to participate in a single test programme with either FOBT or FS.[16, 24] Offering a choice between screening tests may lead to additional uptake, but simultaneously also a loss of participants. The complex decision process, i.e. individuals have to decide on participation to screening and on the preferred test, may lead to uncertainty and non-compliance to the screening programme as a whole. Additionally, the large amount of information subjects will receive on invitation (different tests and their benefits and risks), might withhold subjects without a distinct test preference from attending.

In accordance with other studies we previously found that women were significantly less likely to attend FS screening than men.[12, 13, 15] This study now clearly demonstrated that women refusing FS screening are more likely to attend FIT than men, who refuse FS screening. Countries that implement FS screening should therefore be aware of this potential barrier to participation among women.

A smaller proportion of screenees with a positive screening test attended a colonoscopy (87%) as compared to our population-based data of screenees directly allocated to FIT screening (98%). In this study a similar protocol for referring positive screenees was used.[13] This again suggests that non-participants to FS screening have a negative attitude towards endoscopy and are therefore more likely to refuse a follow-up colonoscopy.

The detection rate of advanced adenoma and CRC in this study mirrors the detection rate in the population-based study in which subjects were directly invited for FIT screening (Table 2; p=0.39).[25] This suggests a similar a priori risk on CRC. Blom et al recently demonstrated that non-respondents to a FS programme have higher risk on CRC than participants, due to unhealthy habits (e.g. smoking).[26] This would be consistent with a higher risk on CRC screening applying for the non-participants of both tests in our trial. However, we could not confirm the data of Blom in our two-recruitment strategy.

A potential limitation of the study is that any reminder has a positive effect on uptake.[27] The additional uptake after a reminder for FS screening was 4%. A small proportion of the additional uptake of FIT screening among non-participants may not be related to test preferences but solely depends on the effect of the reminder. This would expectedly be lower than 4%.

In conclusion, offering FIT screening to non-participants in a FS screening programme increases the overall participation rate considerably, as a quarter of non-participants of FS screening were willing to attend FIT screening. This figure was lower than the participation rate (62%) of a randomised FIT screening arm in the same programme. Women in the target population were more likely to refuse FS screening based on test-related factors. Countries introducing FS screening should be aware of these preferences.

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Chapter 5

Screening for colorectal cancer: comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy

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ABSTRACT

Perceived burden of colorectal cancer (CRC) screening is an important determinant of participation in subsequent screening rounds and therefore crucial for the effectiveness of a screening programme. This study determined differences in perceived burden and willingness to return for a second screening round among participants of a randomised population-based trial comparing a guaiac-based faecal occult blood test (gFOBT), a faecal immunochemical test (FIT), and flexible sigmoidoscopy (FS) screening. A representative sample of the Dutch population (aged 50-74 years) was randomised to be invited for gFOBT, FIT and FS screening. A random sample of participants of each group was asked to complete a questionnaire about test burden and willingness to return for CRC screening. In total 402/481 (84%) gFOBT, 530/659 (80%) FIT, and 852/1124 (76%) FS screenees returned the questionnaire. The test was reported as burdensome by 2.5% of gFOBT, 1.4% of FIT, and 12.9% of FS screenees (comparing gFOBT vs. FIT $p=0.05$; vs. FS $p<0.001$). In total 94.1% of gFOBT, 94.0% of FIT, and 83.8% of FS screenees were willing to attend successive screening rounds (comparing gFOBT vs. FIT $p=0.84$; vs. FS $p<0.001$). Women reported more burden during FS screening than men (18.2% vs. 7.7%; $p<0.001$). FIT slightly outperforms gFOBT with a lower level of reported discomfort and overall burden. Both FOBTs were better accepted than FS screening. All three tests have a high level of acceptance, which may affect uptake of subsequent screening rounds and should be taken into consideration before implementing a CRC screening programme.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related death in Europe.[1] Randomised controlled trials (RCT) provided compelling evidence to support screening of average-risk individuals with faecal occult blood testing (FOBT).[2] One RCT on flexible sigmoidoscopy (FS) screening with seven years of follow-up showed a 59% reduction in CRC-related mortality.[3] Nation-wide screening programmes are currently being implemented in several countries in Europe. In the Netherlands, guaiac-based FOBT (gFOBT), faecal immunochemical test (FIT) and FS are considered as potential screening tests for a nation-wide call-recall screening programme to start in the near future.

Uptake of screening is of considerable importance for the effectiveness of CRC screening programmes. The attendance rate of initial and successive screening rounds has remained low in many countries.[4] Important reasons for non-participation in CRC screening are related to the anticipated burden of a screening test, such as anticipated embarrassment, pain, and discomfort.[4, 5]

Experience with a screening test may affect the willingness to attend successive screening rounds. Given the need for repeated testing at regular intervals (e.g. FS at 5 or 10-yearly periods) to achieve effective screening and the relatively short screening interval of FOBT (annual or biennial) screening, it is of particular importance to determine screening experiences among participants. Additionally, experience with CRC screening may be communicated to other potential screenees, which may also affect uptake of CRC screening programmes in successive cohorts.

A few studies have reported on the test burden of gFOBT and FIT screening.[6-8] Although the perceived test burden of FS screening has been more widely studied [9-12], trials comparing the burden of gFOBT, FIT and FS screening are lacking.

Therefore, this study assessed differences in perceived burden and willingness to return for a second screening round among participants of a randomised population-based trial comparing gFOBT, FIT and FS screening.

METHODS

As part of a Dutch population-based randomised screening trial [13], we evaluated the perceived burden and willingness to return for a successive screening test of various CRC screening tests among participants of gFOBT, FIT and FS screening by means of a questionnaire survey. The trial protocol and data on attendance and diagnostic yield of the different screening methods have been described elsewhere.[13] Recruitment took place between November 2006 and May 2008. The Dutch Ministry of Health approved the study protocol (2006/02WBO). The study questionnaire was approved by the Institutional Review Board of the Erasmus Medical Centre (MEC-2005-264).

Subjects

A random sample of the Dutch population aged 50-74 years was asked to participate in a randomised screening trial.[14] A total of 2375 (uptake: 50%) persons attended gFOBT screening, 2979 (uptake: 62%) persons FIT screening, and 2432 (uptake: 31%) FS screening. A random sample of screenees (481 gFOBT participants, 659 FIT participants and 1124 FS participants) was asked to participate in the questionnaire study on acceptance and burden of the screening test they underwent (Figure 1). For both FOBTs 20-22% of all screenees were selected to participate in this study. For FS a larger proportion of screenees was selected, because power analysis indicated that at least 800 respondents were needed to allow comparative analysis of the prevalence of physical symptoms before and after the FS.

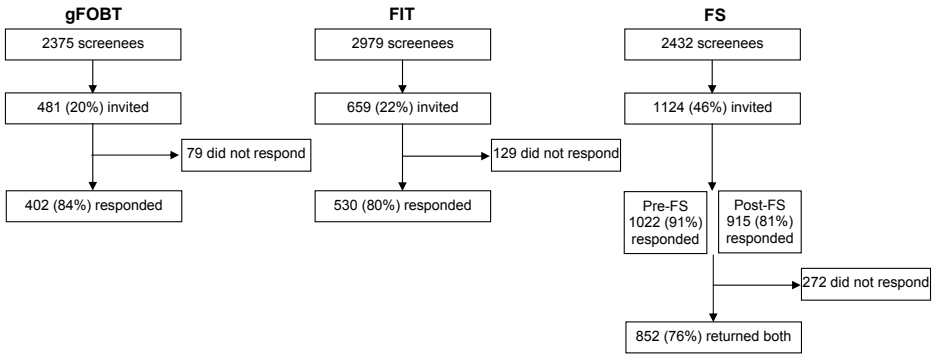

Fig 1: Trial profile

Questionnaires and measurements

gFOBT and FIT screenees were asked to complete a single questionnaire one week after the test was received at the laboratory, but before the screenee received the test result. FS participants were asked to complete a questionnaire in the waiting area of the endoscopy unit prior to their procedure and a second questionnaire one week after the procedure at home. The different components of the questionnaire are discussed below.

Embarrassment, discomfort and pain

Embarrassment and discomfort resulting from FOBT were measured by three separate items that were adapted from earlier studies and related to three stages of the procedure (collecting faeces, performance of the test, and returning the test to the laboratory), each with three response options (not, quite, or very embarrassing/unpleasant).[15, 16]

Pain, embarrassment and discomfort before, during and after the FS were measured one week after the screening test. The four stages of the procedure, i.e. preparation, digital rectal examination (DRE), FS itself, and the period directly after the FS, with three response options (not, quite, or very painful, embarrassing or unpleasant) were assessed separately.

We estimated the overall embarrassment, pain and discomfort for both FOBTS and FS after combining the items into summary scores, by adding the item responses (not = 0, quite = 1, very = 2) per stage of the procedure divided by the number of stages measured.

Overall acceptance

Overall acceptability of the screening method was examined by three items. For each of the three screening tests 5-point Likert scales were used to elicit subjects' perceptions of overall burden of the entire screening procedure ("very burdensome" - "not burdensome at all"), willingness to return for a successive screening round, and whether the participant would recommend friends/family members to undergo the same screening test ("certainly" - "certainly not"). For overall burden, Likert scores of 1-2 were used to indicate burdensome. Likert scores of 1-2 were used to indicate willingness to return for a successive screening round, as well as a positive recommendation to friends/family members to undergo the same screening test, whereas scores of 4-5 were used to indicate not willing to return and a negative recommendation.

Symptoms before and after FS

To detect whether the FS caused physical symptoms, we compared the occurrence of eight symptoms in the week before the test and one week afterwards: rectal blood loss, diarrhoea, constipation, nausea or vomiting, flatulence or feeling bloated, faecal incontinence, anal pain, and abdominal pain. Questions were composed analogous to those of previous studies.[15, 16]

Perceived risk of developing colorectal cancer

We also assessed patients' subjective evaluation of their risk of developing CRC as a potential determinant of the perceived burden, using seven response options (very small, small, quite small, intermediate, quite substantial, substantial, very substantial).[17]

Subject characteristics

Demographic data were collected, including patients' classification of own health using the EQ–5D classification.[18]

Statistical analyses

Statistical analysis was performed using the SPSS statistical package, version 15.0.1. Analysis was performed using the χ^2 test or Student's t-test when appropriate, for nominal and ordinal data. Symptoms before and after FS were compared using McNemar's test. A two-sided p-value of <0.05 was considered significant. Differences between the summary scores of embarrassment, discomfort or pain were calculated using the independent-samples t-test (Cronbach's alphas gFOBT/FIT: α=0.79; FS: α=0.81). The data from the EQ-5D classification of own health were transformed into an EQ-5D index score using the algorithm described by Dolan.[19] Univariate ordinal regression analyses were performed to compare overall burden, recommendation

to friends/family to attend screening, and willingness to return for screening between the three screening tests. To study associations between determinants (screenees age, gender, EQ5D-index score, perceived risk and for FS arm only; previous endoscopy experience, gender of endoscopist) and overall burden, recommendation to friends/family to attend screening and willingness to return we used univariate and multivariate ordinal regression analyses (stepwise inclusion $p < 0.1$). For the subgroup analyses to determine the effect of same-sex endoscopist among women on embarrassment, discomfort and pain during the FS itself a Bonferroni correction was used to compensate for multi-comparison. Spearman's rank correlation was performed to determine the correlation between overall burden and recommendation to friends/family to attend screening and the willingness to return for screening.

RESULTS

Response and respondent characteristics

In total 402/481(84%) gFOBT and 530/659 (80%) FIT screenees returned their questionnaire (Figure 1). Of the FS screenees 1022/1124 (91%) completed the questionnaire prior to the FS and 915/1124 (81%) returned the second questionnaire after the procedure. In total 852/1124 (76%) of FS screenees returned both questionnaires. The respondents' characteristics are shown in Table 1. Characteristics of responding screenees to both FOBT programmes were similar. FS

Table 1: Subject characteristics.

	gFOBT	FIT	FS
Total included screenees (n)	402	530	852
Mean age in years (SD)	60.8 (6.3)	61.6 (6.3)	60.7 (6.4)
Gender (% male)	45.3	50.6	50.7
Ethnicity (% Caucasian)	95.2	95.1	94.5
Marital status (%):			
Married/living with partner	88.7	87.3	88.6
Employment status (%):			
Pensioner/early retirement	35.0	38.9	35.0
In paid work	40.6	38.3	46.9
Unemployed	4.3	4.6	4.3
Education (%):			
Elementary	10.7	12.8	9.3
Secondary	71.8	63.3	64.1
Tertiary and postgraduate	17.6	23.9	26.7
General health, EQ-5D index score: mean (SD)	0.90 (0.13)	0.91 (0.13)	0.93 (0.11)
Endoscopy experience (%)			
Colonoscopy	14.0	15.5	17.1
Sigmoidoscopy	0.5	0.6	1.3
Perceived risk (%)			
Very small - small	43.9	54.1	45.8
Quite substantial - substantial	1.7	3.8	4.0

screenees reported a marginally better general health status as measured by the EQ-5D index score than both FIT and gFOBT screenees (p <0.001), and were slightly older than FIT screenees (p=0.008). All other characteristics including gender, ethnicity, marital, and employment status, level of education, endoscopy experience and perceived risk on CRC were equally distributed between the three screening arms.

Embarrassment, discomfort, and pain

Screenees rated overall embarrassment during gFOBT and FIT equally (0.07 vs. 0.06; p=0.30) (Table 2). A larger proportion of gFOBT than FIT screenees described the test as uncomfortable (0.15 vs. 0.11; p=0.02), mainly due to more discomfort while collecting faeces and performing the test (Table 2).

Table 2: Embarrassment and discomfort per stage of gFOBT and FIT screening.

	gFOBT				FIT				
	Not %	Quite %	Very %	Mean summary Score (SEM)	Not %	Quite %	Very %	Mean summary Score (SEM)	p-value
Embarrassment				0.07 (0.01)				0.06 (0.01)	0.30
Collecting faeces	90.7	8.1	1.3		93.7	6.1	0.2		0.06
Performing the test	94.0	5.8	0.3		95.2	4.8	0.0		0.45
Returning the test	95.7	4.0	0.3		94.6	5.2	0.2		0.14
Discomfort				0.15 (0.01)				0.11 (0.01)	0.02
Collecting faeces	77.1	20.6	2.3		85.1	13.6	1.3		0.00
Performing the test	83.6	15.4	1.0		90.4	8.4	1.1		0.00
Returning the test	96.7	3.3	0.0		96.2	2.9	1.0		0.63

Overall score for embarrassment, discomfort, and pain during FS were 0.18, 0.42, and 0.27, respectively. FS screenees reported embarrassment most frequently during the DRE (quite/very: 24.0%). In total 13.4, 19.3 and 11.0% of screenees reported to have been quite/very embarrassed during the preparation, the endoscopy itself, and the period after the FS, respectively. Pain and discomfort were mainly reported during the endoscopy (quite/very: 55.0 and 53.9%). In total, 17.4 and 15.4% of the screenees experienced the procedure as very painful or uncomfortable (Table 3). The mean overall embarrassment and discomfort were significantly higher for FS than for gFOBT and FIT screening (p <0.001).

Symptoms before and after FS

Undergoing FS screening was not significantly associated with the occurrence of diarrhoea (reported prevalence one week before and one week after FS screening being: 7.4 vs. 6.4%), constipation (4.7 vs. 6.1%), anal pain (5.8 vs. 4.5%), faecal incontinence (1.0 vs. 1.1%), nausea and vomiting (2.6 vs. 2.4%), or rectal blood loss (1.4 vs. 2.8%). Screenees significantly more often reported abdominal pain (9.2 vs. 15.8%; p<0.001), and flatulence or feeling bloated (23.6 vs. 33.4%; p<0.001) one week after than before the FS.

Table 3: Embarrassment, discomfort and pain per stage sigmoidoscopy screening.

	Sigmoidoscopy			
	Not %	Quite %	Very %	Mean summary Score (SEM)
Embarrassment				0.18 (0.01)
Preparation	86.7	12.4	1.0	
Digital rectal examination	76.0	22.1	1.9	
Sigmoidoscopy	80.7	16.9	2.4	
Directly afterwards	89.0	9.8	1.2	
Discomfort				0.42 (0.01)
Preparation	68.6	28.3	3.1	
Digital rectal examination	75.9	22.5	1.7	
Sigmoidoscopy	46.1	38.4	15.4	
Directly afterwards	69.1	25.0	5.9	
Pain				0.27 (0.01)
Preparation	95.5	4.3	0.2	
Digital rectal examination	90.3	8.8	0.8	
Sigmoidoscopy	45.0	37.6	17.4	
Directly afterwards	81.5	15.4	3.1	

Overall acceptance

Significantly less FIT than gFOBT described the test as burdensome (p=0.05), whereas FS was more often reported to be burdensome than gFOBT (p<0.001) and FIT (p<0.001) (Fig 2a). Significantly more women than men reported burden during FS screening (18.2% vs. 7.7%; p<0.001). Younger screenees (<60 years) were more likely to experience test burden during FIT and FS screening than older screenees (≥60 years) (FIT 2.2% vs. 0.7%; p=0.002; FS 15.5% vs. 10.5%; p=0.002), whereas age was not associated with reported burden of gFOBT screening (3.2% vs. 2.0%; p=0.22). Reported burden was higher among screenees with a low compared with a high level of education in all screening arms (gFOBT 8.7% vs. 0.0%; FIT 4.9% vs. 0.0%; FS 11.6% vs. 6.8%; p-values <0.001).

Female screenees reported less burden when the FS was performed by a same-sex endoscopist (22.8 vs.15.5%; p=0.02), while in male screenees no such association was found (8.0 vs. 7.5%; p=0.20). Women less often described the FS itself as embarrassing if the FS was performed by a female instead of a male endoscopist (quite/very: 18.4% vs. 34.4% p<0.001), whereas no differences in pain or discomfort was found. In men no such association was found.

The vast majority of FOBT screenees would encourage friends and/or relatives to attend FOBT screening (gFOBT 96.0%, FIT 95.8%; p=0.76) and was willing to attend a successive screening round (gFOBT 94.1%; FIT 94.0%; p=0.84). A significantly smaller proportion of FS screenees was willing to attend another round of FS screening (83.8%, p-values <0.001) or would encourage friend and/or relatives (FS 87.1%, p-values <0.001) to undergo FS screening compared to both FOBTs (Fig 2b,c). There was a significant correlation between perceived burden and willingness to attend another round (gFOBT ρ –0.38; FIT ρ-0.52; FS ρ –0.50; all p-values<0.001) and a positive recommendation to friends and/or relatives (gFOBT ρ –0.41; FIT ρ-0.40; FS ρ –0.53; all p-values<0.001).

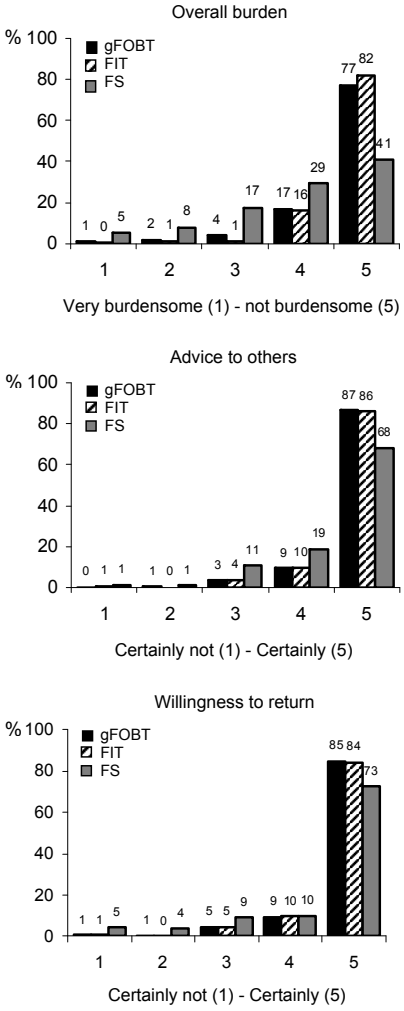

Fig 2: Using a five-point Likert scale: scores on overall burden, the recommendation subjects would give to others to participate in screening, and willingness of screenees to return for successive screening rounds.

Men who underwent a FS were more willing to attend a successive screening round than women (86.4% vs. 78.8%; p=0.014). EQ5D-index score, perceived risk on CRC, and previous endoscopy experience were not significantly associated with experienced burden, recommendation to friends and/or relatives, or with willingness to return for a successive screening round.

DISCUSSION

Population-based screening needs to be well accepted in order to achieve an adequate uptake in first and successive screening rounds. This is the first population-based study comparing

perceived test burden and willingness to return for a successive screening round between gFOBT, FIT and FS in an average-risk population. All three screening tests were well accepted among participants, given the large proportion of screenees willing to return for successive screening rounds and the positive recommendation for screening that most subjects intended to give their family and/or friends. FIT was perceived as slightly less burdensome than gFOBT screening due to less reported discomfort during faecal collection and test performance. The number of faecal samples required may explain the difference in discomfort during faecal collection, as the gFOBT had to be performed on three consecutive bowel movements and FIT was a one-sample test. This is further underlined by an Australian study that showed similar acceptability of FIT and gFOBT when a two-sample FIT was used.[20] The difference in faecal sampling method between gFOBT (card) and FIT (swab) might also clarify the difference in discomfort, as reported by a British study showing that potential screenees preferred a sterile transport swab to a smear card.[21] The higher acceptability of FIT is in line with results of two RCTs, both demonstrating a higher uptake of FIT compared to gFOBT.[22, 23] The higher acceptability is an important argument for choosing FIT in preference to gFOBT as the screening method for a nation-wide screening programme, apart from additional arguments regarding test performance characteristics.[23-26] Therefore, the Dutch Health Council recently recommended introducing a nation-wide FIT-based CRC screening programme.

FS is clearly more burdensome than both FOBTs, as 55% of screenees reported some kind of discomfort or pain. However, in agreement with previous studies only a small proportion of screenees reported severe embarrassment, discomfort or pain during the procedure.[9, 10, 27-29] In this and other studies all FS were performed without conscious sedation, which seems acceptable for FS screenees.[9, 28]

Perceived burden of FS screening varied by gender. Our observations reflect those of other studies reporting that women were more likely to experience burden during FS [30, 31], and were therefore less willing to return for successive screening rounds. This contributes to the reported lower uptake among women for a first FS screening round.[9, 28, 32] A lower uptake in first and successive screening rounds will limit the effectiveness of FS as a screening modality in women. Therefore, endoscopists should be even more aware of potential burden in women, and should consider steps to minimise burden and thereby improve uptake for successive screening rounds (e.g. using sedation or a more flexible, smaller-calibre endoscope).

Several studies have shown a preference for a female endoscopist among women.[33, 34] Nickelson and colleagues revealed embarrassment as the most important reason for preferring a same-sex endoscopist. The present study shows that the expectation reflects the actual experience, as women reported more embarrassment during the FS itself when performed by a female compared to a male endoscopist. A nation-wide screening programme might therefore be more effective when women are offered a choice between a male or female endoscopist.

Our study has shown that preparation with a single enema self-administered at home was well accepted by screenees.[13] A few screenees reported significant embarrassment (1.0%),

discomfort (3.1%) or pain (0.2%) during preparation. Furthermore, as described previously, a high proportion of screenees was willing to perform the bowel preparation at home (85%).[35,36]

The present study showed that the willingness to undergo successive screening rounds was significantly lower for FS screenees than for both FOBTs. Nevertheless, only a small minority of screenees was not willing to attend successive screening rounds of gFOBT (1.2%), FIT (1.3%) or FS (8.3%) screening, which is in line with previous studies.[6, 10, 12, 37] This finding is essential for an effective screening programme, since screening tests must be repeated at regular intervals to be effective. Furthermore, experience with CRC screening will be communicated to other potential screenees. This may largely affect uptake of successive cohorts, given the low level of awareness of CRC and CRC screening in Europe and especially in the Netherlands.[38] In the present study, the majority of respondents would recommend family/friends to undergo screening with the same test they underwent themselves. This will positively affect uptake of screening resulting in increasing uptake levels in successive screening rounds.

A drawback of this study is that, because the majority of respondents were of Caucasian ethnicity (95%), our results can not be extrapolated to a non-Caucasian population. Further studies on test burden in a non-Caucasian population are therefore needed. Furthermore, FS screenees were slightly older than FIT screenees and healthier than both gFOBT and FIT screenees, since those subgroups were more likely to participate in screening. However, these differences in subject characteristics did not affect the interpretation of the results, since these marginal differences are clinically irrelevant. Furthermore, perceived test burden can only be measured in screenees and not in non-participants.

In conclusion, gFOBT, FIT and FS are well accepted screening tests among participants. FIT slightly outperforms gFOBT with a lower level of reported discomfort and overall burden. Both FOBTs were better accepted than FS screening. The high level of acceptance may affect uptake of subsequent screening rounds and should be taken into consideration before implementing a CRC screening programme. Furthermore, attempts should be made to improve acceptance of FS screening among women if FS is considered to be the test of choice, since women reported significantly more discomfort during FS screening.

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Chapter 6

Preferences for colorectal cancer screening strategies; a discrete choice experiment.

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ABSTRACT

Guidelines underline the role of individual preferences in the selection of a screening test, since insufficient evidence is available to recommend one screening test to another. We conducted a study to determine individuals' preferences and to predict uptake for CRC screening programmes with various screening tests. A discrete choice experiment (DCE) questionnaire was conducted among screening naïve and previously screening subjects aged 50-75. Subjects were asked to choose between scenarios based on faecal occult blood test (FOBT), flexible sigmoidoscopy (FS), total colonoscopy (TC) with various test specific screening intervals and mortality reductions, and no screening (opt-out). In total 489/1498 (33%) screening-naïve (52% male; mean age±SD 61±7yrs) and 545/769 (71%) previously screened subjects (52% male; mean age±SD 61±6yrs) returned the questionnaire. Type of screening test, screening interval, and risk reduction of CRC related mortality influenced subjects' preferences (all $p<0.05$). Screening-naïve and previously screened subjects equally preferred five-yearly FS and ten-yearly TC ($p=0.24$; $p=0.11$), but favoured both strategies to annual FOBT screening (all p-values <0.001) if, based on the literature, realistic risk reduction of CRC related mortality were applied. Screening-naïve and previously screened subjects were willing to undergo a ten-yearly TC instead of a five-yearly FS to obtain an additional risk reduction of CRC related mortality of 45% ($p<0.001$). These data provide insight to which extend interval and risk reduction of CRC related mortality affect preferences for CRC screening tests. Assuming realistic test characteristics, subjects in the target population preferred endoscopic screening to FOBT screening partly due to the more favourable risk reduction of CRC related mortality by endoscopy screening. Increasing potential screenees' knowledge on risk reduction by different screening strategies is therefore warranted to prevent unrealistic expectations and to optimise informed choice.

INTRODUCTION

Colorectal cancer (CRC) is the second cause of cancer-related death in the Western world. Screening can reduce CRC related mortality by removal of adenomas and early detection of CRC.[1-5] There is compelling evidence to support screening of average-risk individuals over 50 years of age.[2, 4-7] Guidelines underline the role of individual preferences in the selection of a screening test [8-10], since insufficient evidence is available to recommend one screening test to another. Individual preferences for a certain screening test have been found to influence uptake in a CRC screening programme.[11] Uptake is a key factor determining the effectiveness of such a screening programme. However, uptake levels are fairly low in many countries (<60%).[4, 5, 12-15] Several countries, including The Netherlands, are currently considering introduction of a nation-wide CRC screening programme. It is therefore essential to obtain insight into individual preferences for available screening strategies prior to the implementation of a nation-wide screening programme.

Previous surveys demonstrated a broad variation in preferences for CRC screening tests, since tests differ in benefit (CRC mortality reduction) on the one hand and potential harms on the other hand (perceived burden, complications). Subjects who valued effectiveness most highly chose for colonoscopy screening, whereas others preferred faecal occult blood testing (FOBT) because of the less invasive character.[11, 16-18] These studies however did not provide data on the relative importance of test characteristics on preferences, for example, how much potential health gain does a subject require to undergo invasive endoscopic screening?

Discrete choice experiments (DCEs) are becoming more widely used in health care research.[19-23] A DCE is capable of establishing preferences and to predict uptake in controlled experimental conditions, through responses to realistic and hypothetical scenarios. DCEs may be valuable for patient centred evaluations of health technologies.[24]

This study was conducted to determine individuals' preferences and to predict uptake for CRC screening programmes with various screening tests, and the relative importance of different test characteristics for these preferences in an average risk population. Furthermore, we aimed to identify differences in preference structures between subgroups in the population.

METHODS

Study population

A total of 1498 screening-naïve individuals aged 50-74 years old were randomly selected from municipal registries of the Rotterdam region in the Southwest of the Netherlands. We also invited a random sample of 769 screened subjects of a CRC screening trial comparing guaiac-based FOBT (gFOBT), faecal immunochemical test (FIT) and flexible sigmoidoscopy (FS) (Fig 1). This screening trial was carried out in the same target population as mentioned above.[12]

Age, sex and social economic status were equally distributed among the screening naïve and screening experienced invitees.

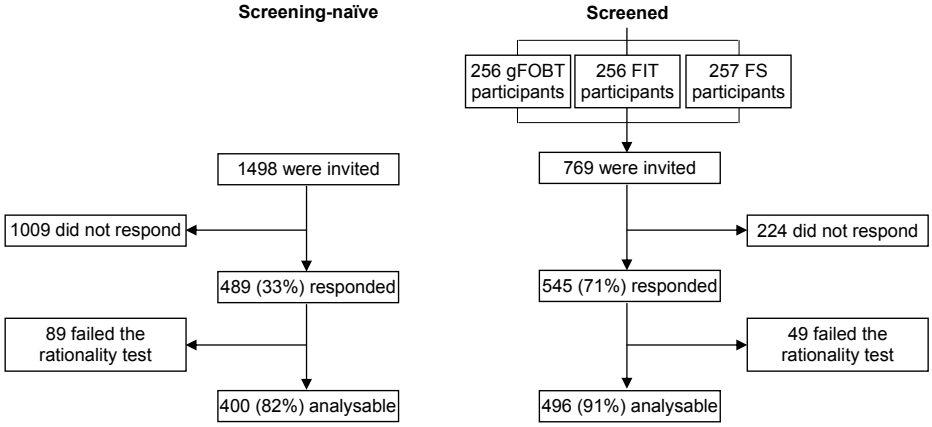

Fig 1: Study profile.

Discrete choice experiments

DCEs can measure individuals' preferences for health care interventions. DCEs are based on the assumptions that a healthcare intervention can be described by its characteristics (attributes) (e.g. frequency of undergoing the intervention) and that the individual valuation of the intervention is determined by pre-defined levels (e.g. monthly, yearly) of those attributes. The health care intervention (e.g., screening test) as well as its test characteristics have to be specified before generating an experimental design. In a DCE individuals choose between several realistic and hypothetical scenarios. Preference estimates can be obtained from the choice data and describe the relative preference for characteristics of the health care intervention.

Attributes and levels

FOBT, FS and total colonoscopy (TC) are most widely used as CRC screening test and therefore incorporated in this study design. The characteristics and their levels were derived from the literature, expert opinions (n=3) and interviews with potential screenees (n=40). Experts were asked to comment on a list of characteristics derived from literature review. Potential screenees could also comment on the list of characteristics and rank them in order of importance. Based on these data we selected the two most important characteristics as identified by both groups: risk reduction of CRC related mortality (RR) and screening interval. Noteworthy, characteristics that are directly related to the test (e.g. oral bowel cleansing solution is not required for FOBT and always for TC) were already captured by the specific screening test (FOBT, FS and TC). All subjects were informed about the incorporated test characteristics of the three screening tests (Appendix 2). The specific values (levels; e.g. amount of risk reduction, or length of screening

interval) for each test characteristic incorporated the range of possible test outcomes of a specific screening test (FOBT, FS and TC) based on the current literature (Table 1). The levels were test specific to create realistic scenarios (Table 1). Levels of risk reduction were presented in the questionnaire as absolute values to reduce framing effects, in accordance to the literature.[25] In the presentation of the results in this paper we used the relative risk on CRC related death, since this is most commonly used in the screening literature (e.g. FOBT 13-18% risk reduction). The absolute risk on CRC related death without screening was set at 3.0%. People aged 50 in the Netherlands have a 3.0% risk of dying from CRC, based on data of the Dutch comprehensive cancer centre. (IKC, www.ikc.nl).

Table 1: Alternatives, attributes and the alternative specific levels based on the literature.

Alternatives	Alternative specific levels	Literature	References
Screening interval (yr)			
FOBT	1/3 - 1 - 3	1 - 2	(2; 3)
Sigmoidoscopy	1 - 5 - 10	5 - 10	(2; 3)
Colonoscopy	2 - 5 – 10	5 - 10	(2; 3)
Risk reduction (%)			
FOBT	10 - 25 - 40	13 - 33	(4-7)
Sigmoidoscopy	40 - 50 - 70	49 - 62	(8-12)
Colonoscopy	75 - 85 - 95	80 - 84	(9; 13)

Study design and questionnaire

The design contained three tests (FOBT, FS and TC) and two characteristics (risk reduction of CRC related mortality and screening interval) with three levels each (Table 1). The test specific levels (e.g. screening interval of FOBT between four months and triennial) were required to select realistic combinations. Furthermore, unrealistic combinations of the characteristics' levels were blocked (i.e. a combination of the lowest RR with the shortest screening interval as well as the highest RR combined with the longest screening interval). The combination of the characteristics and levels resulted in 21 (i.e. 7*3) possible test scenarios, and thus 343 (i.e. 7^3) possible combinations of the scenarios (i.e. full factorial design). It is not feasible to present a single individual with all these combinations. We therefore reduced the design in such away that two-way interactions could be estimated (i.e. we created a fractional factorial design). We therefore used SAS software (Version 9.1, SAS Institute Inc., Cary, NC, USA), which is capable of generating designs that are highly efficient (i.e. maximizing D-efficiency or minimizing D-error) in such circumstances.[26] We chose a design with 84 choice sets divided over 7 versions of the questionnaire (D-error 0.573). Each choice set included two CRC screening tests and an option not to be screened (opt-out) (Appendix 1). A design in which all three screening tests and the option not to be screened were presented was not feasible, since the pilot study (n=20) showed a significant decrease in subjects' understanding and acceptance of the questionnaire.

A rationality test was included in the questionnaire to determine the understanding of the questionnaire by each subject. The rationality test was a choice set of which one screening

option was logically preferred to the other option given the levels of each test characteristic (biennial FS screening resulting in 40% RR against biennial FS screening resulting in 70% RR). It is common practice to exclude irrational responses [27-29], and we therefore adopted this approach. However, some recent discussions in the literature suggest that these responses could be included.[30, 31] Further sensitivity analyses were conducted and inclusion of irrational responses led to similar results.

Subjects' social economic status (SES), previous lower endoscopy experience (sigmoidoscopy or colonoscopy) and experience with CRC in family and close friends were determined. Furthermore, the generic health status (EQ-5D summary score) was assessed. This is a validated classification of subject's own health.[32]

We conducted a pilot study (n=20) to ascertain that subjects could manage the length of the questionnaire and to evaluate subjects' understanding, acceptance and face-validity of the questionnaire and the background information on the three screening tests (Appendix 2). The questionnaire was mailed to all subjects. Background information on the three screening tests was printed on the first page of the questionnaire (Appendix 2). A reminder was sent to non-responders four weeks later.

Data Analysis

Each choice between two tests and the opt-out was considered as a specific observation. The DCE was analysed using multinomial logit regression models with test specific parameters. The model was implemented in SAS software (Version 9.1, SAS Institute Inc., Cary, NC, USA). A priori we expected the test as well as the two characteristics to be important for subjects' choices and that a higher risk reduction and lengthening of 'screening interval' would have a positive effect on preferences.

We assumed that there was no linear relationship between the different levels of the characteristics. Therefore, we estimated the following models for the DCE:

$U_{FOBT} = VFOBT + \varepsilon\ FOBT = \beta 0 + \beta 1\ Interval1yr + \beta 2\ Interval3y\ r + \beta 3\ RR25 + \beta 4\ RR40 + \varepsilon\ FOBT$

$U_{FS} = VFS + \varepsilon\ FS = \beta 5 + \beta 6\ Interval5yr + \beta 7\ Interval10yr + \beta 8\ RR50 + \beta 9\ RR70 + \varepsilon\ FS$

$U_{TC} = VTC + \varepsilon\ TC = \beta 10 + \beta 11\ Interval5yr + \beta 12\ Interval10yr + \beta 13\ RR85 + \beta 14\ RR95 + \varepsilon\ TC$

$U_{no\ test} = 0$

Utility (U) represents the preference for a (hypothetical) CRC screening programme. U consists of the deterministic and observable component (V) and the random component (ε) to the analysis, accounting for unobserved or unobservable components of choice. The observed utility (V) in this study is referred to as preference (V). The absolute value of V has a relative interpretation: the higher the score of V, the stronger a respondent's preference for a particular screening strategy. The constant terms (screening test; $\beta_{0,}\ \beta_{5,}\ \beta_{10}$) are alternative specific constants that indicate the general attitude of subjects towards screening with a specific screening test compared to no screening. $\beta_{1,2'}\ \beta_{6,7,}\ \beta_{11,12}$ are coefficients of the levels of the test characteristic

'screening interval' and $\beta_{3,4}$, $\beta_{8,9,}$ $\beta_{13,14}$ are coefficients of the levels of the test characteristic 'risk reduction of CRC related mortality'; each coefficient indicates the relative weight individuals place on that test specific level compared with the reference level for that test specific test characteristic (for the reference levels see Table 3). A two-sided p-value smaller than 0.05 was considered statistically significant.

Generic health status was dichotomized to an EQ-5D summary score of '1', representing full health, versus an EQ-5D summary score '<1', indicating sub-optimal health. Aggregate data on social economic status (SES) were available at the level of the area postal code (www.cbs.nl) of the subject, weighted by population size and classified into three groups (high, intermediate, low).

Chi-square and Student t-tests were used to assess the differences in the value of characteristics between screening naïve and screened subjects as well as between subgroups (age, gender, SES, EQ-5D, prior endoscopy experience, or knowing someone affected by CRC) within the screening-naïve population.

To examine the predicted uptake of CRC screening based on our results, we applied previously proposed models to our data.[33, 34] We also investigated the effect of changing the characteristics, as identified by the results of our multinomial logit model, on the expected uptake of CRC screening.

Ethical approval

The study was approved by the Institutional Review Board of the Erasmus Medical Centre (MEC-2007-224).

RESULTS

A total of 489/1498 (33%) screening-naïve and 545/769 (71%) screened subjects returned the questionnaire. Screening-naïve subjects were of higher SES than screened subjects (p<0.001, Table 2). A higher proportion of screened subjects previously underwent a lower endoscopy compared to screening-naïve subjects (49% vs. 23%; p<0.001). Among the subjects that participated in the CRC screening trial 22% (70/324) of the screenees that performed a FOBT previously underwent a lower endoscopy and obviously all (172/172) FS screenees.

DCE

A significantly higher proportion of the screened subjects (91%) passed the rationality test compared to the screening-naïve subjects (82%; p<0.001).

Screening-naïve subjects did not prefer FOBT to no screening. They expressed a positive attitude towards FS and TC (positive and statistically significant sign, Table 3, Fig2). A high RR was preferred to intermediate and low RR for all screening tests (p-values <0.01). Screening-naïve subjects expressed a more positive attitude towards an intermediate (FOBT: annually;

Table 2: Subjects' characteristics.

	Screening-naïve subjects	Previously screened subjects	p-value
Analysable subjects	400	496	
Sex (male; n-%)	209 (52)	260 (52)	0.96
Age (mean-SD)	60.7 (6.6)	61.1 (6.4)	0.36
EQ5D score (mean-SD)	0.94 (0.11)	0.93 (0.10)	0.76
Social economic status (n-%)			<0.01
High	195 (49)	196 (40)	
Intermediate	77 (19)	96 (19)	
Low	128 (32)	204 (41)	
Lower endoscopy experience (n-%)			<0.01
Yes	92 (23)	242 (49)	
No	307 (76)	251 (50)	
Unknown	1 (1)	3 (1)	
Knowing someone affected by CRC (n, %)			0.78
Yes	53 (13)	67 (13)	
No	285 (71)	381 (77)	
Unknown	62 (16)	48 (10)	

FS: five-yearly; TC: five-yearly) compared to a short screening interval (FOBT: four monthly; FS: annual; TC: biennial). Further lengthening of the screening interval (FOBT: triennial; FS: ten-yearly; TC: ten-yearly) had only a small positive effect on subjects' preferences for FOBT (p=0.02) and FS (p=0.02), and no effect on subjects' preferences for TC screening.

Screened subjects had a positive attitude towards all screening tests (p<0.001). A high RR was preferred to intermediate and low RR for all screening tests, and an intermediate screening interval was preferred to a short screening interval (Table 3, Fig 2). Screened subjects did not prefer an intermediate to a long interval for all screening tests (FOBT p=0.67; FS p=0.99; TC p=0.10).

Screening-naïve versus screened subjects

Screened subjects had a more positive attitude towards all screening tests than screening-naïve subjects (Table 3, p<0.001). The differences in preferences regarding RR and screening interval between screening-naïve and screened subjects were statistically not significant, except for preferences regarding five- and ten-yearly FS screening. The more positive attitude of screening-naïve subjects towards longer screening intervals (Five-yearly p<0.001; ten-yearly p<0.001) indicated that screening naïve-subjects valued infrequent screening more positively than screened subjects.

Differences in preferences between subgroups

No differences in preferences were found between men and women, apart from a more positive attitude towards TC among men (TC p=0.02). Men, in contrast to women, did prefer FS and TC to no screening (men: FS p<0.001; TC p<0.001; women FS p=0.07; TC p=0.84). Respondents' age, SES and EQ-5D summary score did not influence the attitude towards a screening test, interval

Table 3: Regression coefficients from the discrete choice experiments for the different tests and attributes.

	Screening-naïve subjects		Previously screened subjects		
Attribute levels	Coefficient	(95%CI)	Coefficient	(95%CI)	p-value‡
Screening test (base level 'no screening')					
No screening *(reference level)*					
FOBT	-0.18	(-0.44;0.08)	0.38	(0.15;0.62)*	<0.001
Sigmoidoscopy	0.30	(0.06;0.54)*	0.94	(0.72;1.16)*	<0.001
Colonoscopy	0.33	(0.08;0.57)*	1.05	(0.84;1.27)*	<0.001
Risk reduction of CRC related mortality					
FOBT					
3% to 2.7% (RR 10%) *(reference level)*					
3% to 2.4% (RR 25%)	0.19	(-0.01;0.38)	0.17	(-0.01;0.34)	0.88
3% to 1.8% (RR 40%)	0.78	(0.54;1.02)*	0.65	(0.44;0.87)*	0.45
Sigmoidoscopy					
3.0 to 1.8% (RR 40%) *(reference level)*					
3.0 to 1.5% (RR 50%)	0.10	(-0.09;0.29)	0.33	(0.16;0.50)*	0.08
3.0 to 0.9% (RR 70%)	0.65	(0.42;0.89)*	0.65	(0.44;0.86)*	0.97
Colonoscopy					
3.0 to 0.8% (RR 75%) *(reference level)*					
3.0 to 0.5% (RR 85%)	0.16	(-0.03;0.35)	0.19	(0.02;0.36)*	0.79
3.0 to 0.1% (RR 95%)	0.40	(0.17;0.62)*	0.41	(0.20;0.61)*	0.95
Screening interval					
FOBT					
Four-monthly *(reference level)*					
Annual	0.73	(0.52;0.93)*	0.64	(0.44;0.83)*	0.50
Triennial	0.96	(0.72;1.20)*	0.67	(0.46;0.89)*	0.07
Sigmoidoscopy					
Annual *(reference level)*					
Five-yearly	0.92	(0.74;1.11)*	0.55	(0.39;0.72)*	<0.001
Ten-yearly	1.14	(0.91;1.37)*	0.56	(0.36;0.75)*	<0.001
Colonoscopy					
Biennial *(reference level)*					
Five-yearly	0.71	(0.52;0.90)*	0.56	(0.39;0.73)*	0.22
Ten-yearly	0.72	(0.48;0.95)*	0.42	(0.21;0.63)*	0.06

‡ p-value describes the difference between screening-naïve and screened subjects

* p-value < 0.05 compared to the reference level; Abbreviations: RR: risk reduction; FOBT: faecal occult blood test.

or RR. Subjects who reported to have a close friend or family member with CRC expressed a more positive attitude towards TC screening than subjects without (p=0.01). Experience with FS or TC was positively associated with the willingness to undergo a TC (p<0.001). Subjects that underwent FS screening had a more positive attitude towards FS and TC screening than subjects who performed a FOBT (p<0.001)

Trade-offs

Screening-naïve subjects were, when assuming the same interval (annual) and RR (40%), more willing to undergo FOBT than FS screening (Preference/Observed utility (V) FOBT: V=1.32; FS: V=0.30; p<0.001). Preferences were similar for a five-yearly FS and an annual FOBT if both tests

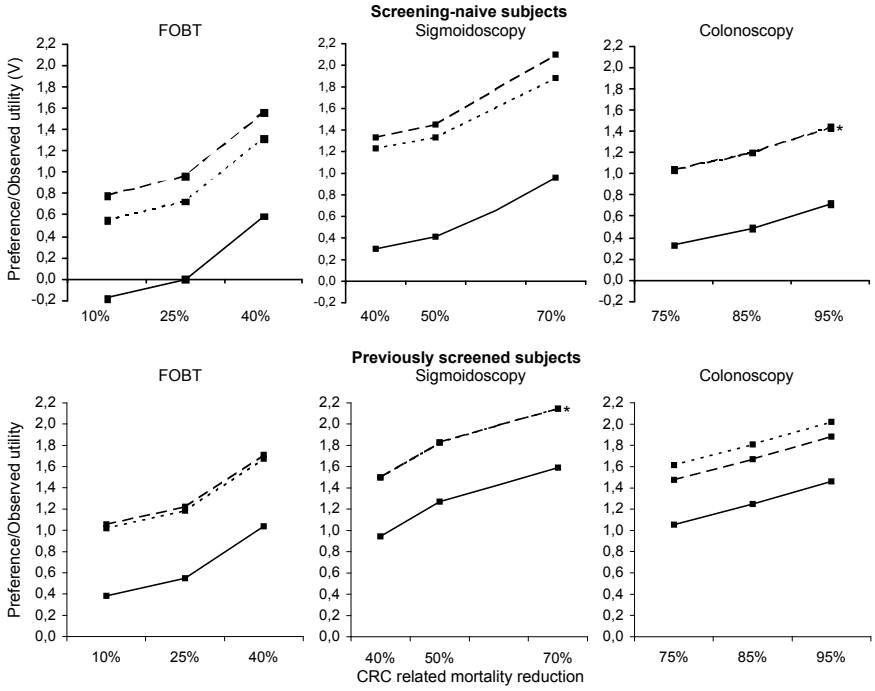

Fig 2: Preferences for the different screening strategies at a long (--), intermediate (···) and short (—) Screening interval and different levels of mortality risk reduction for screening-naïve and previously screened subjects.

would generate a RR of 40% (FOBT: V=1.32; FS: V=1.23; p=0.40). A five-yearly FS was preferred to annual FOBT if FOBT was associated with a less favourable RR than FS screening (FOBT 25% RR: V=0.73; FS 40% RR: V=1.23; p<0.001).

A five-yearly FS was preferred to a ten-yearly TC if the difference in RR was 25% in favour of TC (e.g. FS: RR 50%; TC RR 75%; p<0.001). The preferences for a five-yearly FS and a ten-yearly TC were similar if TC would achieve an additional 35% RR (p=0.24), while more than 45% difference in RR was associated with a preference for 10-yearly TC (e.g. FS: RR 50%; TC RR 95%; p<0.001).

Screening-naïve subjects equally preferred FS and TC screening, but did prefer both endoscopic screening options to FOBT screening if, based on the literature, the most realistic screening intervals and mortality reduction were applied (annual FOBT RR 25%: V=0.73; five-yearly FS RR 50%: V=1.33; ten-yearly colonoscopy RR 85%: V=1.22 ; FS vs. FOBT p<0.001, TC vs. FOBT p<0.001; TC vs. FS p=0.24).

Screened subjects made similar trade-offs between the screening test, interval and RR as screening-naïve subjects.

Predicted uptake

Predicted uptake of screening naïve subjects for FOBT, FS and TC screening was 45%, 58% and 58% respectively, assuming screening with the reference level for RR and screening interval. Based on realistic screening intervals and mortality reduction from the literature, these numbers were 68% for FOBT, 79% for FS, and 77% for TC. The screening programme characteristics had substantial impact on the expected uptake among screening naïve subjects (Figure 3).

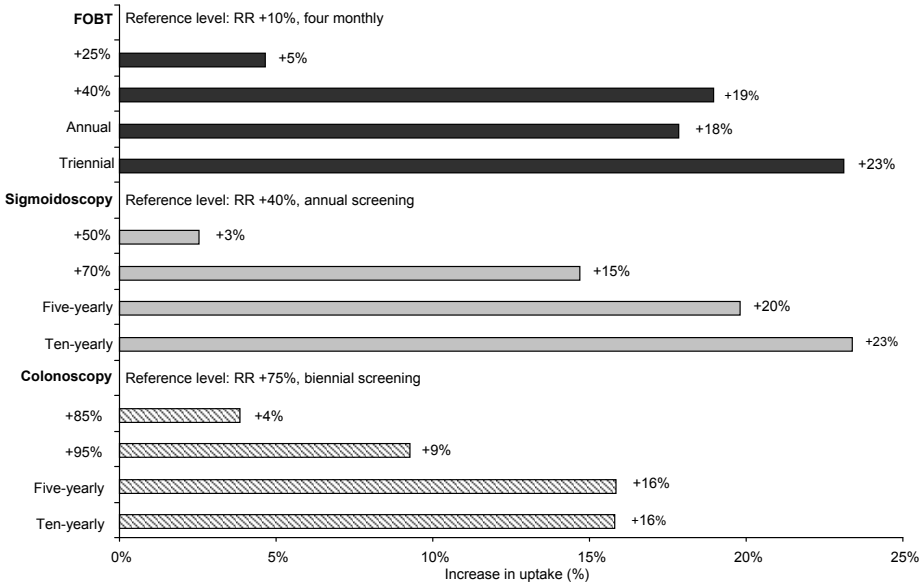

Fig 3: Effects of changing the screening programme characteristics on the average probability of uptake for respectively FOBT (45%), FS (58%) and TC (58%) in screening-naïve subjects.

DISCUSSION

Principle findings

In this population-based study we found that the type of screening test, screening interval, and risk reduction of CRC related mortality significantly influenced individual preferences among screening naïve and screening experienced subjects in the target population (aged 50-74 years old). These data provide insight in the relative importance of the effect of screening interval and risk reduction of CRC related mortality on preferences for the three most commonly used screening tests. Both screened and screening-naïve subjects preferred FS and TC to FOBT screening if, based on the literature the most realistic screening interval and risk reduction on CRC related mortality were applied (annual FOBT with 25% RR; five-yearly FS with 50% RR, ten-yearly colonoscopy with 85% RR).[2, 4-7, 10, 35, 36] This underlines the importance of

adequate information on those aspects of CRC screening to achieve informed decision-making by potential screenees.

Five studies investigated preferences in CRC screening using a DCE [19, 20, 37-39], with two studies investigating preferences among available screening tests.[20, 37] This is the first DCE including both a screening naïve and screening experienced population. In agreement with previous DCE studies, we found that RR dominated preferences for a screening test. Both FS and TC screening were therefore preferred to FOBT screening when associated with sufficient RR.[20, 37]

The literature on preferences for the optimal screening interval per test is limited. One study reported a preference for five or ten-yearly to annual screening irrespective of the screening test.[37] However, deciding on screening interval without information on the screening test leads to unrealistic choices, since an annual FOBT is less burdensome than an annual TC. We therefore used test specific screening intervals, which add to the validity of our results. In our study, screened subjects equally preferred intermediate and long screening interval for all tests. Reassurance may be a reason for preferring frequent screening.[40] However, both intermediate and long interval of all three screening tests were preferred to a short interval, suggesting that subjects trade-off between reassurance and frequency of undergoing a screening test.

Men had a more positive attitude towards FS and colonoscopy screening than women. This finding is in accordance with FS screening programmes which described a lower uptake among women than among men.[12-14] Known barriers for women to participate in endoscopy screening are male endoscopists [41], and anxiety prior to screening.[42] A different approach to inform both sexes on screening or sex-specific screening strategies might be considered in a nation-wide screening programme to improve acceptance.

The results of this study may be relevant to predict population preferences for newer screening tests with a similar profile or an improved version of a screening test. For example, recently randomised trials demonstrated more favourable detection rates for FIT than gFOBT suggesting a larger reduction of CRC related mortality.[12, 15, 43] According to our data, informing people in the target population about a more favourable effect on CRC related mortality of FIT would lead to a higher acceptance of FIT screening and most likely a higher uptake.

Predicted uptake of FS or TC screening based on our model was significantly higher than uptake of FOBT screening, given realistic levels. This finding is in contrast to the observed higher uptake of FOBT than FS screening in the randomised screening trial performed in the same population as this DCE. Screenees in this trial were however not specifically informed on test efficacy. This suggests that increasing awareness on the efficacy of a screening test may enhance uptake. It is therefore of paramount importance to improve the level of awareness on achievable risk reduction of CRC related mortality to obtain a higher uptake, especially for the more effective endoscopic screening tests. This is further underlined by two European studies. A Swiss study, in which the majority (75%) of all screenees chose to undergo a TC, and only a small proportion (25%) preferred FOBT or FS screening after they were informed about the efficacy of

the three screening tests.[44] A large population-based Italian study found similar participation rates for FS and FOBT when subjects were offered a choice between both strategies.[45]

Strengths and weaknesses of this study

In contrast to previous DCE studies we used a labelled instead of an unlabelled DCE design. In a labelled design the specific screening test is mentioned in each choice option (FOBT, FS, TC; appendix 1), while in an unlabelled design the screening test is presented as 'screening test 'A', 'B' or 'C' and is further described by certain characteristics that are presented in the choice set. CRC screening tests may evoke individual feelings, which can not be described in a questionnaire (e.g. anxiety for an endoscopy). It is therefore difficult to adequately convey the essential differences from a subject's perspective between FOBT and endoscopic tests in terms of, for example, 'more burdensome' or 'less burdensome'. Using a labelled design, the scenarios are more realistic, which adds to the validity of the results. Furthermore, we assessed preferences among screening-naïve and screened subjects within the target population (aged 50-74 yrs old) including all social economic classes, which add to the generalisability of the results. Experienced subjects stated a more positive attitude towards all screening tests than screening-naïve subjects. A selection bias may explain this difference in attitude, as experienced subjects have already demonstrated interest in screening and therefore express a more positive attitude towards screening. There is however also an experience effect, i.e. anticipated discomfort and pain might be higher than actually experienced. This experience might reduce anticipated pain and discomfort for successive screening round. Additionally, there may also be an expose effect, i.e. people tend to develop a preference merely because they are familiar with it. Our results suggest that subjects who underwent screening are willing to return for a successive screening round, which is of vital importance for efficacy of a screening program. Costs of screening were not included as a test characteristic in this study. All CRC screening programs in Europe including the Netherlands do not require out-of-pocket costs. Including cost would therefore influence the results in an unrealistic manner. A limitation of this study is the significantly lower response rate in screening-naïve than in screened subjects. This may have led to selection bias. Non-respondents may have a more negative attitude towards screening than respondents. Our results may therefore reflect a more positive attitude than exists in the general population as a whole. The method of framing the levels of risk reduction may have influenced our results. However, we minimised the framing effect in accordance to the literature by presenting absolute values in the questionnaire.[25] It is common practice to exclude irrational responses from the analysis [27-29], and that was why this approach was adopted here. Ryan et al recently postulated that researchers should be cautious when excluding respondents, who failed the rationality test.[30] Additional information on respondents' considerations for failing the rationality test is required. The usage of a "think aloud technique" in the group of subjects who failed the rationality test to determine truly irrational responses has been suggested.[30, 31]

Further research on the effects of excluding subjects based on additional information on failing the rationality test is needed to adopt this approach as common practice.

Conclusions

This data provide insight to which extend interval and risk reduction of CRC related mortality affect preferences for CRC screening tests in the experienced and screening naïve subjects. Both screening-naïve and screened subjects stated a more positive attitude towards both endoscopic screening strategies than FOBT if, based on the literature, the most realistic screening interval and risk reduction on CRC related mortality were applied. Risk reduction of CRC related mortality determined preferences for endoscopic screening. This underlines the importance of awareness on achievable risk reduction of CRC related mortality of the different screening test to enhance uptake particularly for endoscopic screening tests and to optimise informed choice.

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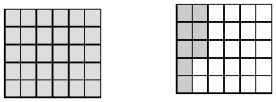
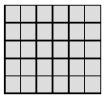
Choice options:	The test you will be examined with:	In the following 10 years you will undergo the test:	The chance of dying from colon cancer decreases from:
A	Sigmoidoscopy	1x	3% to 1,8% 
B	Colonoscopy	1x	3% to 0,8% 
C	None	0x	3% 

Suppose screening for colon cancer is introduced.
Which situation do you prefer? *(fill in: A, B or C)*

Appendix 1: Choice set.

Appendix 2: background information on all screening test as applied to all subjects.

	Faecal occult blood test	Sigmoidoscopy	Colonoscopy
Preparation	**None.**	- One or two enemas (bowel preparation). - No fasting.	- You have to drink 4 litres of special cleansing solution the day before the procedure. - You have to fast for 12 hours prior to the procedure. - You cannot work the afternoon prior to and the day of the procedure.
The procedure	**How do I carry out the test?** At home, you collect a small amount of faeces of 1-3 bowel movements using a test set (see picture). You can return the test by mail to the laboratory. **What does the test measure?** The test measures if there are (in)visible traces of blood present in the stools. **What happens if the test results are abnormal?** You will be advised to undergo a colonoscopy.	**The procedure** ***The last 60 cm of the large bowel*** is examined by using a flexible tube with a small camera on the tip. This tube is inserted through the anus. During the procedure the large bowel will be filled with air in order to carefully examine the bowel. **What do I feel of the investigation?** Because of the air put into your bowel you may feel abdominal cramps. **What happens if abnormalities are found?** Precursors of colon carcinoma (polyps) are removed during the procedure (this is painless). You will be advised to undergo a colonoscopy to see if there are other abnormalities in the remainder large bowel.	**The procedure** You will be given conscious sedation ('short narcosis'). Therefore, you may fall into a light sleep. T*he entire large bowel (100-120 cm)* is examined by using a flexible tube with a small camera on the tip. This tube is inserted through the anus. During the procedure the large bowel will be filled with air in order to carefully examine the bowel. **What do I feel of the investigation?** Due to the air and tube in your bowel you may feel abdominal pressure and cramps. **What happens if abnormalities are found?** Precursors of colon carcinoma (polyps) are removed during the procedure (this is painless).
After the procedure	- You can return to your daily activities immediately.	- You may eat and drink again immediately and go home.	- You may eat and drink again and go home after one hour. - You cannot drive a car, ride a motorcycle or bicycle.
Perceived burden	Low.	High.	High.
Results	- You will receive the result by mail within two weeks.	- Directly after the procedure. - When tissue has been removed, you will receive the pathology results by mail within two weeks.	- Directly after the procedure. - When tissue has been removed, you will receive the pathology results by mail within two weeks.
Test at home or in the hospital	At home.	Hospital.	Hospital.
Total duration of the procedure	30 minutes.	15 minutes.	1 hour and 45 minutes.
Complications	Never.	In 1 in 10.000 individuals: severe blood loss or a perforation or a tear through the bowel wall.	In 1 in 1.000 individuals: severe blood loss or a perforation or a tear through the bowel wall.

Chapter 7

What determines individuals' preferences for colorectal cancer screening programmes? A discrete choice experiment.

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ABSTRACT

In many countries uptake of colorectal cancer (CRC) screening remains low. We aimed to assess how procedural characteristics of CRC screening programmes determine preferences for participation and how individuals weigh these against the perceived benefits from participation in CRC screening. A discrete choice experiment was conducted among subjects in the age-group of 50–75 years, including both screening-naïve subjects as well as participants of a CRC screening programme. Subjects were asked on their preferences for aspects of CRC screening programmes using scenarios based on: pain, risk of complications, screening location, preparation, duration of procedure, screening interval and risk reduction of CRC related death. The response was 31% (156/500) for screening-naïve and 57% (124/210) for CRC screening participants. All aspects proved to significantly influence the respondents' preferences. For both groups combined, respondents required an additional relative risk reduction of CRC related death by a screening programme of 1% for every additional 10 minutes of duration, 5% in order to expose themselves to a small risk of complications, 10% to accept mild pain, 10% to undergo preparation with an enema, 12% to use 0.75 litres of oral preparation combined with 12 hours fasting and 32% to use an extensive bowel preparation. Screening intervals shorter than 10 years were significantly preferred to a 10-year screening interval. This study shows that especially type of bowel preparation, risk reduction and length of screening interval influence CRC screening preferences. Furthermore, improving awareness on CRC mortality reduction by CRC screening may increase uptake.

INTRODUCTION

Colorectal carcinoma (CRC) is the second most frequently occurring malignancy in the European Union, and the second leading cause of cancer related death in the Western world.[1] A recent study demonstrates that for many European countries CRC mortality rates are decreasing while incidence is rising, suggesting an increasing CRC prevalence.[2] CRC screening is effective in reducing CRC mortality.[3-11] Screening can reduce CRC mortality by early detection of CRC and endoscopic removal of premalignant precursors of CRC (adenomas).[5, 6, 12] There are several methods available for CRC screening. The various types of faecal occult blood tests (FOBTs) primarily aim at the early detection of CRC, whereas endoscopic and radiologic screening tests (flexible sigmoidoscopy (FS), colonoscopy) are effective at both early detection and removal of premalignant lesions.[12] Different screening methods are expected to have a different impact on CRC mortality reduction due to these differences in preventive potential. CRC screening methods also differ with respect to procedural characteristics, which determine the subject's burden of a screening method. CRC screening methods perceived as the most burdensome (FS, colonoscopy) also have the largest potential for prevention of CRC.[12] Currently, insufficient evidence is available to recommend one screening method over another.

Attendance is an important determinant of the effectiveness of CRC screening programmes. Uptake of CRC screening in a pilot screening programme in the Netherlands has remained lower than uptake of breast and cervical cancer screening.[13-15] In many other countries, uptake of CRC screening, as well as continuing adherence to CRC screening, has also remained suboptimal.[3, 4, 13, 16-18] It has been established that increasing colorectal cancer screening uptake, in comparison with other targets, has a large potential for reducing CRC related mortality.[19] Attendance rates depend on the willingness of individuals to undergo a certain screening test. This willingness may be influenced by perceived advantages and drawbacks of CRC screening tests and furthermore, by knowledge and awareness of CRC, CRC risk and CRC screening.[16, 20, 21] Individuals may be willing to undergo a screening test despite several drawbacks in order to maximize health benefit or vice versa (to accept a lower health benefit in order to avoid several burdensome test characteristics). To optimise a CRC screening programme it is of paramount importance to gain insight in factors that influence population preferences for CRC screening programmes, and the trade-offs individuals are willing to make between benefits and drawbacks of a CRC screening programme. Research has shown that patient preferences can have a major impact on their willingness to use services and furthermore, there is an increasing emphasis on involvement of patients in health care decisions.[22]

This study therefore investigated preferences for CRC screening using a discrete choice experiment (DCE). DCE is a survey methodology with its origin in market research. DCEs are widely used for the assessment of preferences in transport and environmental economics and marketing research.[23] They are increasingly used for health care purposes.[24, 25]

It has been demonstrated that awareness of CRC and CRC screening in the Netherlands has remained low.[26] There is currently no organised CRC screening programme in the Netherlands, except for hereditary or familial CRC. A similar situation is encountered in many countries in the EU, in fact, only approximately 50% of the target population is offered any type of screening for CRC. It is of particular importance to study preferences in a screening naïve population, since they may guide the introduction and adjustment of new CRC screening programmes in these countries.

The aim of our study was to determine how procedural characteristics of various CRC screening methods determine preferences for participation, and how individuals weigh these against the expected health benefits from CRC screening. We compared the relative importance of aspects of the three most commonly used CRC screening tests: FOBT, FS and colonoscopy.

MATERIALS AND METHODS

Study population

We conducted the study in two groups. The first group included a total of 500 screening-naïve individuals aged 50-74 years old who were randomly selected from the population registry of the region Rijnmond in the Southwest of the Netherlands. The region includes Rotterdam and surrounding suburbs and harbours 338000 inhabitants in the target age groups. The second group included 210 participants of a randomised screening trial for CRC in the Netherlands from the same target population as mentioned above. This screening trial invited average risk individuals to participate in a CRC screening programme with guiac-based FOBT (gFOBT), faecal immunochemical test (FIT) or FS.[13]

Invitation of subjects

Subjects were contacted by mail. They received a questionnaire and an information brochure with general and background information about CRC and CRC screening. Individuals could return the questionnaire in a postage-paid self-addressed envelope that was included in the mailing package. A reminder was sent four weeks later in case of non-response.

DCE

DCE is a formal technique to assess preferences, assuming that a healthcare intervention (e.g. a screening programme) can be described by its characteristics (attributes; e.g. test duration).[27] Those attributes are further specified by variants of that attribute (levels; e.g. for test duration: 10, 20, 30 minutes). The DCE assumes that the individual preference for a test is determined by the levels of those attributes.[27] Individuals are presented with a number of choice sets containing several scenarios (screening programmes). Those programmes are described by several attributes with varying levels (Figure 1). The results of a DCE provide information on the relative

importance of the attributes and the trade-offs individuals are willing to make between these attributes. The DCE design will be explained in more detail further on.

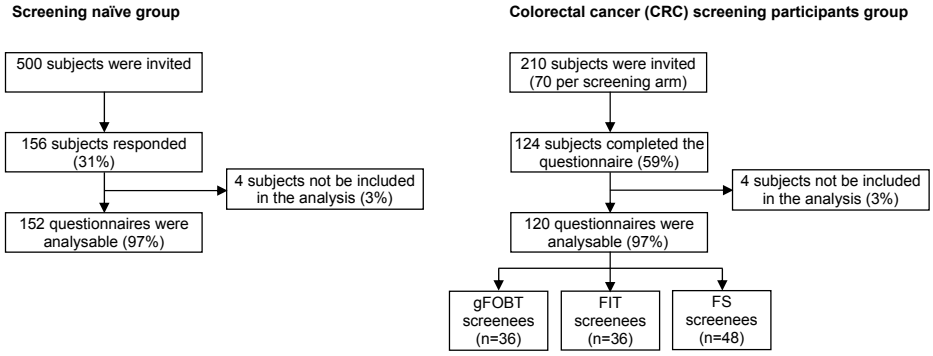


Fig 1: Choice set example

Attributes and attribute levels

The attributes and attribute levels of the DCE were derived from literature review, expert opinions, interviews with screening naïve (n=10) and screened (n=10) individuals of the target population. In the interviews we asked individuals to point out which of these attributes they expected to be important or had been important in their decision to participate in a CRC screening programme. The attributes identified as most relevant were: pain, risk of complications, location of the screening test, preparation for the procedure, duration of the procedure, screening interval and risk reduction of CRC related death (Table 1). Attribute levels were derived from the literature. The levels for each attribute incorporated the range of characteristics or possible test outcomes of all different screening methods (FOBT, FS and colonoscopy). The attribute 'interval' was related to a CRC screening programme, the other attributes were test-related.

Study design and questionnaire

The design contained three attributes with two levels and four attributes with four levels. The combination of those attributes and levels resulted in 2048 (i.e. 2^3*4^4) possible test scenarios. Since it is not feasible to present a single individual with all these scenarios, we reduced the model to 16 scenarios (a fractional factorial design) by means of a website, containing a library of orthogonal arrays.[28] These 16 scenarios were used to create 16 choice sets. Each choice set contained two screening programmes and an opt-out (the option to choose 'no screening', see figure 1). A special technique (fold-over; [29]) was used to create the second programme of each choice set. As a result, our design was an efficient orthogonal design; there was no correlation between any pairs of attributes (orthogonality), all levels of each attribute were represented in the same frequency (level balance), and similar levels of an attribute did not occur within the same choice set (minimal overlap). A rationality test was included in the DCE to investigate the

Table 1: Attributes and levels for colorectal cancer (CRC) screening

Attributes and levels	Beta coefficients in regression analysis
Pain	
No pain *(reference level)*	
Mild pain	β_1
Risk of complications	
None *(reference level)*	
Small	β_2
Location	
At home *(reference level)*	
Hospital	β_3
Preparation	
None *(reference level)*	
Enema. no fasting	β_4
Drinking of 0.75 litre of fluid. 12 hours fasting	β_5
Drinking of 4 litres of fluid. 18 hours fasting	β_6
Duration	
10 minutes	β_7
30 minutes	
60 minutes	
90 minutes	
Interval	
1x in 10 years *(reference level)*	
2x in 10 years	β_8
5x in 10 years	β_9
10x in 10 years	β_{10}
Risk reduction of death from CRC	
3% → 2.7% (10% relative risk reduction)	β_{11}
3% → 1.8% (40% relative risk reduction)	
3% → 1.2% (60% relative risk reduction)	
3% → 0.3% (90% relative risk reduction)	

understanding of the questionnaire. This was a choice set of which one screening programme was logically preferable over the other given the attribute levels.

The questionnaire further contained questions on background variables (e.g. generic health status (EQ-5D; [30]) and a question assessing experienced difficulty of the questionnaire (5-point scale). A written description of the attributes and levels was given at the beginning. We conducted a pilot study (n=20) to ascertain respondents could manage the length of the questionnaire and to examine the intelligibility, acceptability and validity of the questionnaire.

The study was approved by the Medical Ethical Committee of the Erasmus Medical Centre (MEC-2007-224).

Analyses

Each choice between three options (two screening programmes and the opt-out) was considered as a specific observation. A multinomial logit model was used to analyse the data. We excluded individuals who answered less than 13 questions of the DCE.

We assumed that there was no linear relationship between the different levels of the attributes 'preparation' and 'screening interval' and that all attributes had independent effects on preferences. On this basis, we estimated the following model for the DCE:

$$U= V + \varepsilon = \beta_0 + \beta_{1\ pain} + \beta_{2\ complications} + \beta_{3\ location} + \beta_{4\ enema} + \beta_{5\ 0,75lfluid} + \beta_{6\ 4lfluid} + \beta_{7\ duration} + \beta_{8\ interval2} + \beta_{9\ interval5} + \beta_{10\ interval10} + \beta_{11\ mortalityreduction} + \varepsilon$$

U represents latent utility of a CRC screening alternative in a choice set. It is assumed that an individual will choose the CRC screening alternative which maximises his/her utility amongst all alternatives in a choice set. V is a systematic, explainable, component specified as a function of the attributes of the CRC screening alternatives. ε is the random (unexplainable) component representing unmeasured variation in preferences. The constant term (screening programme; β_0) is an 'alternative specific constant' and indicates the relative weight individuals place on screening programmes compared to no screening. β_1-β_{11} are coefficients of the attributes indicating the relative weight individuals place on a certain attribute(level). The value of each coefficient represents the importance respondents assign to a certain level. However, different attributes utilise different units of measurement. For example, the coefficient for 'risk reduction of death from CRC' represents the importance per relative 10% risk reduction. When looking at a screening programme that generates a 50% risk reduction, the coefficient should be multiplied five times in order to enable comparison to the coefficients of other levels. An attribute with a two sided p-value smaller than 0.05 was considered to be important in the decision to participate in a certain screening programme.

Given the current DCE literature [31, 32], further sensitivity analyses were conducted to explore the impact of excluding respondents who failed the rationality test by removing such individuals from the sample and rerunning the analysis.

The trade-offs respondents were willing to make between the attributes were calculated by the ratios of the coefficients of the different attributes with risk reduction as the denominator. For example, β_1/β_{11} indicates how much additional relative risk reduction respondents think a test should generate in order to undergo a test that causes mild pain instead of a test that causes no pain.

To examine the expected uptake of CRC screening based on our results, we applied the model as presented by Gerard and colleagues and Hall and colleagues to our data. [33, 34]

$$\frac{1}{(1+e^{\wedge -V})}$$

The model assumes that a preference score of 0 indicates that individuals have an equal preference for either participation or non-participation, hence the expected participation rate equals 50%. Additionally, we investigated the effect of changing the most important CRC screening programme characteristics, as identified by the results of our multinomial logit

model, on the expected uptake of CRC screening. The average probability of participation was calculated by entering the constant term (β_0) into the model as described above.

The expected uptake of the different screening tests was calculated by adding up the different levels corresponding with the screening test concerned, and entering this value into the model. The levels we applied for assessing the uptake of FOBT were 'no pain', no risk of complications, location 'at home', no preparation and a duration of 15 minutes. For FS we applied 'mild pain', a small risk of complications, location 'hospital', preparation by an enema and a duration of 30 minutes. For colonoscopy we used 'mild pain', a small risk of complications, location 'hospital', preparation by 'drinking of 4 litres of fluid and a duration of 90 minutes.

The influence of the different levels on expected uptake was calculated by entering the coefficients of the levels, added to the constant term, into the model.

Aggregate data on socio-economic status (SES) were available at the level of the respondents' area zip code, weighted by the number of inhabitants per postal code and classified into three groups (high, average, low).

Characteristics of the different groups were compared using parametric and non-parametric tests. For categorical data, we used Chi-square and Fisher Exact Test to test for differences between screening naïve individuals and CRC screening participants. For continuous variables, we used the Independent Samples T-Test. To assess whether there were differences in preferences among participants of the FOBT (either gFOBT or FIT) and FS screening programme and those with and without endoscopy experience, we performed subgroup analyses. For comparing subgroups, we included all respondents in the same model and used the subgroup as interaction term.

RESULTS

Respondents

The response rate was higher among CRC screening participants (59%; 124/210) compared to screening naïve individuals (31%; 156/500) (Table 2). The characteristics of the respondents are shown in Table 2. Among the screening naïve group, 22% had undergone an endoscopy in the past. Within the group of CRC screening participants, 53% had previous endoscopy experience including 22% (16/72) of FOBT screenees and logically all FS screening subjects (48/48).

DCE RESULTS

Forty-three percent of the screening-naïve individuals and 50% of the CRC screening participants rated the questionnaire as 'easy' (p=0.24).

Table 2: Respondent characteristics

Characteristics	Screening naïve	Participants	Difference
Response (n respondents/n invited - %)	156/500 (31.0)	124/210 (59.0)	p<0.01
Analyzable questionnaires (n - %)	152 (97.4)	120 (96.8)	p=0.74
Age (mean – standard deviation (SD))	59.9 (5.7)	62.2 (6.4)	p<0.01
Gender (male; n - %)	74 (48.7)	59 (49.2)	p=0.94
Socio economic status (n - %)			p=0.49
High	78 (51.3)	53 (44.2)	
Intermediate	21 (13.8)	20 (16.7)	
Low	53 (34.9)	47 (39.2)	
Endoscopy experience (n - %)			p<0.01
Yes	33 (21.7)	64 (53.3)	
No	117 (77.0)	54 (45.0)	
Unknown	2 (1.3)	2 (1.6)	
Knowing someone affected by colorectal cancer (CRC)			p=0.84
(n - %)	19 (12.5)	18 (15.0)	
Yes	115 (75.7)	88 (73.3)	
No	18 (11.8)	14 (11.6)	
Unknown			
Generic health status (EQ-5D) summary score (mean - SD)	0.92 (0.11)	0.93 (0.12)	p=0.48

The signs of all coefficients of the attributes were consistent with our initial hypotheses (see Table 3). The positive sign given to the coefficient 'risk reduction of death from CRC' indicated that respondents preferred a test generating a higher risk reduction over a test that generates a lower risk reduction. The positive sign of the coefficients for shorter screening intervals indicated that individuals preferred those screening intervals over screening once every 10 years. The negative signs for all other attributes indicate that individuals preferred a screening test of shorter duration, with no preparation, no pain and no risk of complications.

The non-significant coefficient of the constant term in the screening-naïve group indicated that these subjects had, if assuming a screening programme with the reference level for all the attributes, no preference for either screening or no screening whereas the group of CRC screening participants expressed a positive attitude towards screening compared to no screening (positive significant coefficient). All screening attributes proved to be important determinants of the preferences in each of the respondent groups, except for location of the screening test, which only significantly influenced preferences of CRC screening participants and not those of the screening naïve individuals and a preparation with '0.75 litres of fluid and 12 hours fasting', that did not influence preferences of CRC screening participants.

The results of the sensitivity analyses indicated that removing respondents who failed the rationality test did not entail drastic changes in the outcomes of those analyses. We therefore included them in our further analyses.

The differences in preferences *between* screening naïve-individuals and participants of a CRC screening programme were statistically not significant, except for preferences regarding risk reduction of CRC related death. Screening naïve individuals demanded more effectiveness from a CRC screening programme compared to participants (p<0.01). We performed subgroup analyses, analysing FOBT and FS screenees separately, which showed that participants of FOBT

Table 3: Preferences of the screening naïve individuals and participants of a colorectal cancer (CRC) screening programme

Levels	Screening naïve		Participants	
	β-coefficient	95% confidence interval	β -coefficient	95% confidence interval
Constant (screening)	0.25	(-0.00 to 0.50)	0.62	(0.35 to 0.90)*
Pain				
No pain (ref)				
Mild pain	-0.31	(-0.42 to -0.20)*	-0.23	(-0.34 to -0.11)*
Risk of complications				
None (ref)				
Small	-0.16	(-0.28 to -0.05)*	-0.13	(-0.25 to -0.01)*
Location				
At home (ref)				
Hospital	-0.09	(-0.20 to 0.02)	-0.01	(-0.13 to 0.10)*
Preparation				
None (ref)				
Enema. no fasting	-0.37	(-0.57 to -0.16)*	-0.23	(-0.45 to -0.02)*
Drinking of 0.75 liter of fluid. 12 hours fasting	-0.51	(-0.72 to -0.29)*	-0.22	(-0.45 to 0.01)
Drinking of 4 liters of fluid. 18 hours fasting	-0.98	(-1.18 to -0.77)*	-0.88	(-1.10 to -0.67)*
Duration				
None				
Per 10 minutes spent in the screening process	-0.03	(-0.05 to -0.01)*	-0.03	(-0.06 to -0.01)*
Interval				
1x in 10 years (ref)				
2x in 10 years	0.28	(0.11 to 0.45)*	0.24	(0.06 to 0.42)*
5x in 10 years	0.40	(0.21 to 0.59)*	0.33	(0.13 to 0.53)*
10x in 10 years	0.33	(0.18 to 0.49)*	0.27	(0.10 to 0.44)*
Risk reduction of death from CRC				
None				
Per relative 10% risk reduction	0.32	(0.29 to 0.35)*	0.26	(0.24 to 0.29)*

* significant at the 5% level
(ref) = reference level

and FS screening did differ in preferences: FS screenees expressed a positive attitude, while FOBT screenees expressed a negative attitude towards a test in the hospital ($p<0.001$). Furthermore, FS screenees attached more importance to a 5-yearly screening interval ($p=0.01$) and to the effectiveness of a screening test ($p<0.001$) than FOBT screenees.

When comparing those with previous endoscopy experience to those without endoscopy experience, it could be seen that pain had a significant greater influence on preferences for those without previous endoscopy experience ($p=0.02$). The location hospital was negatively associated with preferences for those without endoscopy experience, but it had a positive affect on preferences for those who had undergone a previous endoscopy (difference: $p<0.01$). Individuals without endoscopy experience also demanded more effectiveness from a screening test ($p<0.01$).

Screening-naïve individuals and CRC screening participants significantly preferred no preparation to all other preparations (p-values <0.03). Both groups significantly preferred preparation with an 'enema' or '0.75 litres of fluid' instead of a preparation with '4 litres of fluid'

Table 4: Individuals' tradeoffs between risk reduction and different aspects of a colorectal cancer (CRC) screening programme

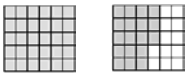
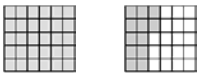
Levels	Screening naïve	Participants	Interpretation note
	% of additional relative risk reduction respondents think a test should generate....		
Pain			.. in order to undergo a test that causes mild pain instead of a test that causes no pain
None (ref)			
Mild pain	10% (6-13%)	9% (4-13%)	
Risk of complications			.. in order to undergo a test that carries a small risk of complications instead of a test with no risk of complications
None (ref)			
Small	5% (1-9%)	5% (0-10%)	
Preparation			.. in order to accept a test that requires a preparation with one of these three methods instead of a test requiring no preparation at all
No preparation (ref)			
Enema. no fasting	11% (2-5%)	9% (1-17%)	
Drinking of 0.75 liter of fluid and 12 hours fasting	16% (9-23%)	8% (0-17%)	
Drinking of 4 liters of fluid and 18 hours fasting	30% (24-37%)	33% (25-41%)	
Duration			.. in order to accept a test with an additional 10 minutes of duration compared to the standard duration
None			
For each additional 10 minutes spent in the screening process	1% (0-2%)	1% (0-2%)	
Interval			.. if the screening interval is lengthened from one of the shorter, more preferred, screening intervals (5-yearly, biennial, annual) to the longest screening interval (once every 10 years)
1x in 10 years (ref)			
2x in 10 years	9% (3-14%)	9% (2-16%)	
5x in 10 years	12% (7-18%)	13% (5-20%)	
10x in 10 years	10% (5-15%)	10% (5-16%)	

(ref) = reference level

(p-values <0.001). Preparation with an 'enema' and '0.75 litres of fluid' were valued equally by both groups (p-values>0.09).

Trade-offs

It can be seen in Table 4 that, based on the expressed preferences, screening-naïve individuals required an additional relative risk reduction of 30% (95% confidence interval (CI) 24-37%) for participation in a screening programme with a test requiring a preparation with '4 litres of fluid and 18 hours fasting' instead of a test that required 'no preparation'. Respondents preferred shorter screening intervals and they were willing to give up a 12% (CI 7-18%) relative risk reduction if the screening interval was *shortened* from once every 10 years to a 2-yearly screening interval. Participants of a CRC screening programme made trade-offs that were comparable to those of the screening naïve individuals.

Choice options:	A	B	C
Preparation:	Enema, No fasting	Drinking of 0.75 liters of fluid, 12 hours fasting	None
Location:	At home	Hospital	None
Pain:	None	Mild pain	None
Risk of complications:	None	Small	None
The chance of dying from colon cancer decreases from:	3% to 1.8% 	3% to 1.2% 	3% 
In the following 10 years you will undergo the test:	5x	2x	0x
Duration:	30 minutes	60 minutes	None

Suppose screening for colon cancer is introduced.
Which test do you prefer? *(Fill in: A. B or C)*

Fig 2: Overview of subjects accessing the study

Expected uptake of CRC screening

The average expected uptake of CRC screening was 56% (CI 50 - 62%) for screening naïve individuals. Assuming that all screening tests would generate a 10% risk reduction of CRC related death, uptake would be 72% for biennial FOBT screening, 46% for 5-yearly FS screening and 22% for 10-yearly colonoscopy screening. We would expect that, if individuals are aware of the achievable risk reduction as currently known from the literature, the uptake would increase to 75% for biennial FOBT screening, 80% for five-yearly FS screening and 71% for 10-yearly colonoscopy screening (risk reduction of CRC related death respectively 16% [35], 59% [6] and 74.5% [36]). The effects of changing the CRC screening programme characteristics on average expected uptake of CRC screening are shown in Figure 3.

DISCUSSION

Our study demonstrates the importance of several procedural characteristics of CRC screening programmes for the preferences of potential and actual screenees: risk reduction of CRC-related death, preparation for the procedure, procedure related pain and complications and screening interval. To optimise a screening programme, the attendance rate should be high. A high attendance rate is only possible when the utilised screening strategy and the information given connect with the preferences of the target population. The results of this DCE in the first place indicate targets for improvement of CRC screening programmes. Secondly they stress the importance of several aspects of screening programmes regarding the information provided to screening invitees. To our knowledge, this is the first study assessing preferences for CRC screening among both screening-naïve subjects and CRC screening participants.

In our study, especially mortality reduction had an important positive influence on preferences for CRC screening methods. A few other studies have investigated preferences for CRC screening using a DCE.[37-42] Our finding that individuals attach much importance to CRC mortality reduction by a screening method is consistent with the results of previous studies.[38, 42, 43] The finding that individuals are prepared to undergo more burdensome screening tests if this results in sufficient additional risk reduction of CRC related mortality demonstrates that they trade benefits and harms of a screening test.

The burden of the required preparation was considered the main drawback of undergoing CRC screening. A preparation commonly used for colonoscopy (i.e. drinking 4 litres of fluid and 18 hours fasting) would only be chosen when an additional relative risk reduction of, on average, 33% would be achieved. In line with our results, Canadian investigators found that preparation was ranked as the most important process related attribute. In contrast, American investigators found that preparation was rated as the least important attribute.[37] The levels that were chosen for the attributes may explain those differences. The results of our DCE are of utmost importance when for example starting a colonoscopy screening programme with a burdensome preparation. Emphasis should be laid on adequate information that should be provided to the target population about the burden and benefits including expected CRC mortality reduction by colonoscopy screening, since this may compensate for a burdensome preparation.

Interestingly, we found that respondents significantly preferred shorter screening intervals to a 10-year screening interval irrespective of health benefit. This finding is consistent with a previous study suggesting that women preferred shorter (annual and biennial) over longer (3-, 4- or 5-year) screening intervals for cervical cancer screening.[44] One study among Danish individuals and another among both American and Canadian individuals could not confirm preferences for shorter CRC screening intervals.[38, 39] A second American study could not determine if individuals preferred shorter or longer screening intervals.[37] Several studies have showed that reassurance may be a motivation for and/or a result of undergoing cancer screening.[45, 46] The preference for shorter screening intervals found in our study may be associated with expected reassurance. This again stresses the importance of adequate information provided to potential screenees. It emphasises the need to adequately inform individuals that longer screening intervals for CRC screening do not imply lower reductions in mortality, but that specific CRC screening tests with longer screening intervals have more potential for CRC prevention and therefore require less frequent testing.

There were some differences in preferences between FOBT and FS screenees. Assessment of preference variations across subgroups is advisory because of status quo bias; in other words the tendency of people to value services higher once they have experienced them.[47] We conducted the study among both screening-naïve individuals and individuals who had prior experience with CRC screening tests, so that we were able to investigate if status quo bias was present. The preferences of screening-naïve subjects and CRC screening participants were not significantly different. The fact that FOBT screenees expressed a negative attitude towards

a test in the hospital, while FS screenees expressed a positive attitude towards a test in the hospital may be explained by the phenomenon of status quo bias. However, it may also be a result of selection bias; that those subjects with a preference for the location 'home' do not participate in FS screening and vice versa. Interestingly, the same significant difference regarding the influence of screening location on preferences was observed when comparing those with endoscopy experience to those without. A possible explanation might be that individuals on beforehand have a negative association with the location hospital, but develop a positive attitude towards a hospital-based examination once they have experienced it.

Research has consistently shown that expected pain is one of the most important reasons for declining the endoscopic screening offer.[16, 48, 49] The results from our study confirm that finding and furthermore they demonstrate that pain has significant less influence on preferences of those with endoscopy experience, suggesting that pain actually experienced during endoscopic screening is not as severe as expected on beforehand.

This study revealed uptake levels of the FOBT, FS and colonoscopy based on the characteristics in our model. The uptake levels for FOBT and FS as predicted by our model are somewhat higher than observed in the Dutch screening trial conducted in the same target population [13], however participants in this trial were not informed on achievable risk reduction of CRC related death and the required frequency of testing for FOBT and FS which have both shown to positively influence CRC screening preferences. We found that mainly risk reduction of CRC related death highly influenced the participation that could be expected for the different screening tests, suggesting that increasing awareness on efficacy of the screening tests might enhance uptake.

Given the low levels of awareness of CRC screening in the Netherlands, it may be of vital importance to raise knowledge on achievable risk reduction of CRC related death in order to increase screening uptake especially for the more effective endoscopic screening tests. The importance of awareness on efficacy of the available screening tests is further underlined by data of a Swiss study, in which 75% of all screenees chose to undergo a colonoscopy and only 25% preferred FOBT or FS screening after they were informed about the efficacy of all screening methods.[50] This study involved testimonies from patients with CRC in their campaign in order to raise CRC awareness. This strategy has also been used in various other campaigns throughout the European Union, among others in the United Kingdom, Germany and the Netherlands. CRC patients and their relatives may be important advocates for raising awareness, and possibly also for increasing public familiarity with endoscopic screening which has been demonstrated to influence CRC screening preferences in our study.

There are some limitations to our study. There was a significant difference in response rate between screening-naïve individuals and CRC screening participants. This may have given a selection bias and thereby be a limitation regarding the interpretation of our results.

Furthermore, the way we framed the information on risk reduction may have influenced our results. In order to minimise framing effects we attempted to frame our information, where possible, according to the current literature.[51]

In conclusion, individuals are willing to trade-off benefits and harms of CRC screening programmes. Especially type of bowel preparation, length of screening interval and mortality reduction influenced individuals' trade-offs. The results provide insight in the decision-making process regarding the decision to participate in a CRC screening programme. This information can be used to improve information provided to CRC screening invitees, and identify targets for increasing participation rates.

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Chapter 8

Inter-observer variation in the histological diagnosis of polyps in colorectal cancer screening

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ABSTRACT

We aimed to determine the interobserver variation in the histological diagnosis of colorectal polyps. 440 polyps were randomly selected from a colorectal cancer (CRC) screening program. Polyps were first evaluated by a general (324 polyps) or expert (116 polyps) pathologist, and subsequently re-evaluated by an expert pathologist. Conditional agreement was reported and interobserver agreement was determined by using Kappa statistics. In 421/440 polyps (96%) agreement for the non-adenomatous or adenomatous nature was obtained, corresponding with a very good kappa of 0.88. Differentiating adenomas in non-advanced and advanced obtained consensus in 266/322 adenomas (83%), with a moderate kappa of 0.58. For the non-adenomatous or adenomatous nature, both general and expert pathologists, and expert pathologists among each other, showed very good agreement (kappa-values (95%CI); 0.89 (0.83-0.95) and 0.86 (0.73-0.98), respectively). Categorizing adenomas in non-advanced and advanced showed moderate agreement between general and expert pathologists, and between expert pathologists (kappa-values (95%CI); 0.56 (0.44-0.67) and 0.64 (0.43-0.85), respectively). General and expert pathologists demonstrate very good interobserver agreement for differentiating non-adenomas and adenomas, but only moderate agreement for non-advanced and advanced adenomas. The considerable variation in the interpretation of advanced histology suggests that less subjective criteria are needed for risk stratification in screening and surveillance guidelines.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death in the Western world.[1, 2] The detection and removal of adenomatous colorectal lesions reduces CRC incidence and mortality.[3, 4] Advanced adenomas have a greater likelihood of malignant transformation and development of metachronous adenomas than non-advanced adenomas.[5] Conversely, hyperplastic lesions carry minimal risk of adenoma occurrence.[6, 7]

Histopathological diagnosis of colorectal lesions plays a crucial role in patient management and surveillance after polypectomy. Postpolypectomy surveillance guidelines stratify patients in high and low risk according to their risk of an advanced neoplasia at subsequent colonoscopy. Current guidelines recommend surveillance colonoscopy 3 years after removal of an advanced adenoma or 3 or more adenomas, and 5 to 10 years after removal of 1 or 2 non-advanced adenomas.[8] Histopathologic assessment is also vital in screening for CRC. Advanced adenomas are considered the surrogate biological marker for CRC risk and are the primary target of screening.[9] As many countries have implemented or are considering nation-wide CRC screening[10, 11], accurate pathologic assessment of colorectal lesions is of paramount importance with influence on intensity, burden, cost-efficacy, and potentially outcome of CRC screening.

Concern has been expressed about the reproducibility of the histological interpretation, between general and between expert gastrointestinal pathologists.[12, 13] The aim of the present study was to evaluate inter-observer variation in histological diagnosis of colorectal polyps detected in a CRC screening program. Furthermore, inter-observer variation was assessed between general and expert gastrointestinal pathologists, and between expert gastrointestinal pathologists.

METHODS

Study setting

As part of a Dutch population-based randomized screening trial (CORERO I trial) we randomly selected 440 polyps. The CORERO I study has been described in detail elsewhere [14]. In brief, this randomized population-based trial compared uptake and diagnostic yield of guaiac based faecal occult blood test (g-FOBT), faecal immunochemical test (FIT) and sigmoidoscopy (FS) screening for CRC. Recruitment took place between November 2006 and November 2007. In total 15011 individuals aged 50-74 years old aged 50-74 were 1:1:1 randomized to be invited for gFOBT, FIT or FS screening. Participants with a positive gFOBT (Hemoccult II) or FIT (OC-Hemodia Latex; ≥50 nanogram haemoglobin/ml) were referred for colonoscopy. Participants to FS screening were referred for colonoscopy when one of the following criteria was met:

presence of a polyp with a diameter ≥10 mm; an adenoma with villous histology (≥25% villous) or high-grade dysplasia; three or more adenomas; ≥20 hyperplastic polyps; or invasive CRC.

Sampling procedure and organization

All polyps detected at sigmoidoscopy or colonoscopy, were removed. The interobserver evaluation was conducted on 440 randomly selected polyps. For initial pathological evaluation, 324 polyps were evaluated by a general pathologist (n=23), and 116 polyps were evaluated by an expert gastrointestinal pathologist (n=1). Subsequently, the 440 samples were blindly re-evaluated by an expert gastrointestinal pathologists (n=2).

CRITERIA FOR PATHOLOGIC CLASSIFICATION

The WHO classification was adopted to classify the selected polyps as non-adenomatous or adenomatous.[15] Adenomatous lesions were further categorized according to histologic type, degree of dysplasia, and presence of infiltrating carcinoma. Tubular adenomas were defined as adenomas containing less than 25% of a villous component. Adenomas containing 25% - 75% and more than 75% of a villous structure were defined as tubulo-villous and villous adenoma, respectively. The degree of dysplasia was classified as low or high grade dysplasia. According to the revised Vienna criteria, patients with intramucosal carcinoma or carcinoma in situ were classified as having high-grade dysplasia.[16] Advanced adenomas were defined as adenomas of at least 10mm, or as adenomas with villous histology (≥25%villous) or with high-grade dysplasia. CRC was defined as the invasion of malignant cells beyond the muscularis mucosa and was classified according to the TNM classification.[17-19]

Statistical analysis

Descriptive statistics were used to analyze and report the data. Conditional agreement was reported using percentages. Inter-observer agreement was determined by using Cohen κ statistics, which are widely used mathematical coefficients adjusting for agreement by chance alone. A value of 0 indicates no agreement better than what would be expected by chance alone. Values of < 0.21, 0.21–0.40, 0.41–0.60, 0.61–0.80 and >0.80 correspond to poor, fair, moderate, substantial and very good inter-observer agreement, respectively.[20] The histological diagnoses were categorized as non-adenomatous or adenomatous. Adenomatous lesions were further categorized as non-advanced or advanced based on histology only. For further categorization, the degree of dysplasia was classified as low or high grade dysplasia. Adenomas were categorized as tubular adenoma or adenoma with >25% villous component. In addition, inter-observer agreement between a general and expert pathologist, and between expert pathologists was assessed. Statistical analysis was performed using the SPSS 15.0 program (SPSS Inc. Chicago, IL). A two-sided p-value of ≤ 0.05 was considered statistically significant.

RESULTS

The interobserver agreement between pathologists in the histological diagnosis of colorectal polyps is summarized in Table 1. In 421 out of 440 polyps (96%) agreement for the non-adenomatous or adenomatous nature of polyps was obtained, corresponding with a very good kappa of 0.88 (95% CI; 0.83 - 0.94). More specifically, there was consensus for 99 non-adenomatous and 322 adenomatous polyps. Categorizing the 322 adenomatous lesions in non-advanced and advanced adenomas obtained consensus in 266 adenomas (83%), including 198 non-advanced adenomas and 68 advanced adenomas. Inter-observer agreement for classifying adenomas as non-advanced or advanced was moderate with a kappa of 0.58 (95% CI; 0.48 – 0.68).

Table 1: Inter-observer agreement between pathologists.

	n	Agreement, n (%)	K-values (95% CI)
Non-adenomatous / Adenomatous polyps	440	421 (96%)	0.88 (0.83 - 0.94)
Non-advanced / Advanced adenoma	322	266 (83%)	0.58 (0.48 – 0.68)
Low grade / High grade dysplasia*	322	304 (94%)	0.62 (0.46 – 0.79)
Tubular / Tubulo-villous and villous adenoma	315	259 (82%)	0.55 (0.44 – 0.66)

***** including carcinoma in situ and intramucosal carcinoma.

Among the 322 adenomatous polyps, agreement for low or high grade dysplasia was obtained in 304 polyps (94%), corresponding with a kappa of 0.62 (95% CI; 0.46 – 0.79). There was consensus for 287 low grade and 17 high grade dysplastic neoplastic lesions. Pathologists agreed that five high grade neoplastic lesions had intramucosal carcinoma or carcinoma in situ, but for two high grade dysplastic neoplasms there was no agreement in the classification; high grade adenoma vs. intramucosal carcinoma or high grade adenoma vs. carcinoma in situ. Pathologists did not find carcinoma invading the submocusa or beyond in any of the samples. Categorising the 315 adenomas (without intramucosal carcinoma or carcinoma in situ) as tubular adenoma or as adenoma with >25% villous component, obtained consensus in 259 polyps (85%). Pathologists agreed on 203 tubular adenomas and 56 adenomas with >25% villous histolology giving a kappa-value of 0.55 (95% CI; 0.44 – 0.66). Overall consensus for categorising polyps in non-adenoma or adenoma, histological type and grade of dysplasia was obtained in 336/440 polyps (76%).

Agreement: general vs. expert pathologists, and between expert pathologists

Table 2 summarizes the inter-observer agreement between a general and an expert pathologist on the one hand, and between two expert pathologists on the other hand. Both groups showed very good interobserver agreement in categorizing polyps as non-adenomatous or adenomatous. The general and expert pathologist agreed on 310/324 polyps (96%), including 80 non-adenomatous and 230 adenomatous polyps. This corresponded with a kappa of 0.89 (95% CI; 0.83 - 0.95). The two expert pathologists agreed on 111/116 polyps (96%). There was

Table 2: Inter-observer agreement between general (GP) and expert pathologists (EP), and between expert pathologists (EP`s).

	GP and EP K-values (95% CI)	EP and EP K-values (95% CI)	Combined K-values (95% CI)
Non-adenomatous / Adenomatous	0.89 (0.83 - 0.95)	0.86 (0.73 - 0.98)	0.88 (0.83 - 0.94)
Non-advanced / Advanced adenoma	0.56 (0.44 - 0.67)	0.64 (0.43 - 0.85)	0.58 (0.48 - 0.68)

consensus for 19 non-adenomatous and 92 adenomatous polyps, corresponding with a kappa-value of 0.86 (95% CI; 0.73 – 0.98).

Categorizing adenomas in non-advanced and advanced adenomas showed moderate agreement between general and expert pathologists, and between expert pathologists. The general and expert pathologist agreed on 184/230 adenomas (80%), including 128 non-advanced adenomas and 56 advanced adenomas. The kappa for differentiating non-advanced and advanced adenomas was 0.56 (95% CI; 0.44 - 0.67). The expert pathologists agreed on 82/92 adenomas (89%). There was consensus for 70 non-advanced adenomas and 12 advanced adenomas, corresponding with kappa 0.64 (95% CI; 0.43 – 0.85).

DISCUSSION

This study reported the inter-observer variation in the histological diagnosis of colorectal polyps detected in a CRC screening program. Our data demonstrated that pathologists had very good inter-observer agreement in categorizing polyps as non-adenomatous or adenomatous (kappa-value 0.88). This level of concordance was better than observed by Yoon et al [13], but consistent with other studies.[12, 21-24] In addition our results showed that inter-observer agreement was only moderate for differentiating between non-advanced and advanced adenomas (kappa-value 0.58). More specific, pathologists had moderate agreement for the interpretation of grade of dysplasia and villous histology. In line with our results, several studies also found a poor to moderate agreement for the classification of grade of dysplasia and villous histology. These studies however did not specifically investigate agreement after stratifying adenomas as non-advanced and advanced.[12, 13, 21-26]

Furthermore, our results showed that the inter-observer variability in the classification of colorectal polyps was comparable between general and expert pathologists one the one hand, and between expert pathologists on the other hand. This is in agreement with previous studies.[12, 13, 21-26] In addition, in other fields of pathology it was also found that expert pathologists are just as likely to disagree as general pathologists.[27-29]

Our data confirm that the assessment of advanced histology is subjective.[12, 13, 21-26] This has clinical impact in adenoma less than 10 mm, as adenoma of at least 10 mm are already classified as advanced adenoma. A recent systematic review in a screening population detected advanced adenomas in 5.6% of subjects, adenomas less than 10 mm represented 12.5% of advanced adenomas.[30]

The subjective advanced histologic criteria, more specific villous histology and grade of dysplasia, are of influence on patient management and postpolypectomy colonoscopy surveillance [8]. Misclassification of patients as low risk may postpone colonoscopy surveillance with the risk of missing preventable cancer. Misclassification of patients as high risk may impose further burden on the limited endoscopic resources.[31-36] Postpolypectomy surveillance is the most common reason for performing colonoscopy. Approximately 22% of all colonoscopies are performed for surveillance.[37] It has been suggested that the current postpolypectomy surveillance guidelines have limited predictability for advanced adenoma recurrence.[38] A risk profile based on cumulative findings from multiple previous colonoscopies might better stratify patients in high and low risk than the adenoma findings from the most recent examination.[39] In addition, recent evidence indicates that other factors besides the histological diagnosis, are stronger associated with the development of metachronous advanced adenomas. A pooled multivariate analysis of postpolypectomy patients showed that after four years of follow-up, the risk of metachronous advanced colorectal neoplasia was strongly associated with the number, size, and location of prior adenomas, as well as patient age. In the multivariate analysis, the presence of villous histology was only modestly associated, and the grade of dysplasia was not associated with metachronous advanced neoplasia.[40] In addition, the level of inter-observer variability needs to be considered in the context of the outcome of current studies and colorectal cancer screening programs. Colorectal cancer screening programs rely on advanced adenoma as intermediate endpoint.

In conclusion, this study demonstrated that pathologists have a very good inter-observer agreement for differentiating between non-adenomatous and adenomatous polyps, while the agreement is only moderate for non-advanced and advanced adenomas. Agreement is comparable between general and expert pathologists on the one hand, and between expert pathologists on the other hand. These results show that it is important to modify the criteria for advanced neoplasia or to use other objective and quantitative criteria for the risk prediction, surveillance recommendations, outcome of studies and colorectal cancer screening programs.

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Chapter 9

Cost-effectiveness analysis comparing a quantitative immunochemical test at different cut-off levels with a guaiac faecal occult blood test

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ABSTRACT

Screening with a guaiac faecal occult blood test (gFOBT) has been shown to reduce the mortality from colorectal cancer by 15-33% while being cost-effective. Immunochemical FOBT has been introduced more recently. Two recent Dutch randomised trials (n=30,000) compared gFOBT with quantitative faecal immunochemical testing (FIT) and found a higher attendance and detection rate for FIT (OC-Sensor micro, Eiken, Japan). We aimed to compare the cost-effectiveness of both tests and to identify the most cost-effective FIT cut-off level for referral to colonoscopy. We used the validated MISCAN-Colon micro-simulation model to estimate costs and effects of different screening strategies comparing gFOBT with FIT at cut-off levels of 50, 75, 100, 150 and 200 ng haemoglobin/ml. Screening strategies varied with respect to age range and screening interval. FIT resulted in lower costs and more (quality adjusted) life-years gained than gFOBT. FIT screening was most cost-effective if the 50 ng/ml cut-off level was used. Biennial screening between ages 55 and 75 using FIT at 50 ng/ml resulted in an incremental cost-effectiveness ratio of 3900 euro per life-year gained. Widening the age range to ages 50 and 80 was more cost-effective than shortening the screening interval to one year (5800 versus 14900 euro per life-year gained). In the sensitivity analyses, 50 ng/ml remained the most cost-effective FIT cut-off level. FIT screening is more cost-effective than gFOBT screening. For FIT, a low cut-off level of 50 ng/ml is preferred to higher cut-off levels, including the 100 ng/ml recommended by the manufacturer.

INTRODUCTION

Randomised controlled trials have shown that screening for colorectal cancer (CRC) with faecal occult blood tests (FOBT) reduces CRC mortality with 15-33% in the general population.[1-3] These trials have been performed with the Hemoccult II test, a guaiac-based FOBT (gFOBT). Faecal immunochemical tests (FIT) have become available more recently. Most of the (European) countries with a national screening programme use gFOBT.[4] Several countries consider changing to FIT, now that evidence accumulates that FIT is superior to gFOBT both with respect to attendance rate and diagnostic yield.[5-7]

Screening with gFOBT has been shown to be cost-effective.[8] The additional costs of substituting gFOBT with FIT in a biennial screening program in France have been estimated at 3000 euro per life-year gained.[9] A cost-effectiveness analysis based on data directly comparing both tests is lacking. Such data have recently become available in the Netherlands, where implementation trials have been performed to compare the attendance, positivity and detection rates and costs of gFOBT and FIT. In these trials individuals aged 50-74 were randomised to a gFOBT (Hemoccult II, Biopharma, Weesp, the Netherlands) or a quantitative FIT (OC-Sensor micro, Eiken, Tokyo, Japan).[6, 7] Because the FIT is a quantitative test, it is possible to choose the cut-off level for referral to colonoscopy. The recommended cut-off level (by the manufacturer) is 100 ng heamoglobin/ml. In both trials the FIT cut-off level used for colonoscopy referral was set at 50 ng/ml, so that analyses of test characteristics could be performed for levels of 50 ng/ml and above. We used the trial results in a cost-effectiveness analysis to compare gFOBT and FIT at different cut-off levels, varying the screen interval and the age range.

METHODS

MISCAN-Colon

The MISCAN-Colon micro-simulation model and the data sources that inform the quantification of the model are described in detail in the Appendix, in previous publications [10, 11] and in a standardized model profile.[12] In brief, the model simulates the relevant biographies of a large population of individuals from birth to death, first without screening and subsequently with the changes that would occur under the implementation of a screening program. In every individual one or more adenomas may arise and some of them may develop into cancer. Adenomas can progress from small (1-5 mm) to medium (6-9 mm) to large (10+ mm). The majority of adenomas is assumed to be non-progressive and will never develop into cancer. The progressive adenomas have the ability to become cancer but not all of them will make it to cancer due to competing death of other causes than CRC. The adenomas that become malignant transform into stage I cancers and may successively progress to stage II, III and IV until they are diagnosed in one of these stages. After diagnosis, the individual will die or not

from CRC, depending on the stage specific survival, and again, the competing death from other causes (first death counts). This completes the life history without screening. The same life history is simulated in the situation with screening. An individual with an adenoma or cancer has a chance of having it detected during a screening round depending on the sensitivity of that test for that lesion. After a person is detected with adenomas or CRC, he is referred for colonoscopy for removal of adenomas and diagnosis of cancers. In this way, CRC incidence or CRC death can be prevented. The life-years gained by screening are calculated by comparing the model predicted life-years lived in all the individuals with and without screening.

The model simulated the Dutch population in 2005 (Statistics Netherlands, www.cbs.nl), with cancer incidence based on Dutch data from 1999-2003 (Comprehensive Cancer Centre (CCC), www.ikcnet.nl). Survival after clinical diagnosis of a cancer was based on relative survival data from 1985-2004 from the South of the Netherlands (CCC), since national data were not available. The survival for individuals aged 75 or older was adjusted to fit the observed increasing mortality/incidence ratio (CCC).

The validity of the model has been tested on the results of large screening and surveillance studies, such as the randomised FOBT trials in Minnesota, Funen and Nottingham [13], the CoCap sigmoidoscopy study [10], and the National Polyp Study.[14] Finally, the model was able to explain observed incidence and mortality trends in the US when accounting for risk factor trends, screening practice and chemotherapy treatment.[15]

Test characteristics

We assumed that the sensitivity of gFOBT for CRC was dependent on the time until a cancer becomes clinically diagnosed based on an earlier analysis using the MISCAN-Colon model calibrating on three FOBT-trials.[13] Other test characteristics were chosen to meet the positivity and detection rates as observed in the Dutch trials [5-7, 16] (Tables 1 and 2), while assuming that the sensitivity of FIT for CRC is also dependent on the time until diagnosis.

Screening Strategies

We simulated screening in the Dutch population over a period of 30 years starting in 2005 for in total 48 combinations varying by:

Age to start screening:	45, 50, 55, 60
Age to stop screening:	70, 75, 80
Screen interval:	1, 1.5, 2 and 3 years

After a positive FOBT a diagnostic colonoscopy was offered. If no adenomas were found at colonoscopy, an individual was offered a next FOBT after 10 years. If one or more adenomas were found at colonoscopy, the adenomas were removed and the individual entered surveillance according to the Dutch guidelines [17]: A next colonoscopy was offered after 6 years in case

Table 1: Model assumptions: test characteristics of gFOBT and FIT at cut-off levels 50, 75, 100, 150 and 200 ng/ml.

Test	Specificity (per person, %)	Sensitivity* (per lesion, %)				
		Adenoma ≤ 5 mm	Adenoma 6-9 mm	Adenoma ≥ 10 mm	CRC long before clinical	CRC short before clinical
gFOBT	98.9	0	1.3	6.5	18.2	50.8
FIT 200	98.7	0	2.0	10.6	46.0	80.0
FIT 150	98.3	0	2.3	12.2	47.0	81.0
FIT 100	97.8	0	4.0	13.0	51.0	83.0
FIT 75	97.0	0	4.1	15.2	56.0	85.5
FIT 50	95.8	0	8.4	16.7	61.0	88.0

*Excluding the probability that an adenoma or cancer is found due to the lack of specificity.

Table 2: Modelled (observed) positivity rates and detection rates per 100 screened individuals (highest grade finding per individual) for gFOBT an FIT at cut-off levels 50, 75, 100, 150 and 200 ng/ml.

Test	Positivity rate	No Findings	Non advanced adenomas	Advanced adenomas*	CRC
gFOBT	2.5 (2.5)	98.5 (98.5)	0.35 (0.33)	0.98 (0.97)	0.20 (0.24)
FIT 200	3.7 (3.7)	97.6 (97.6)	0.48 (0.48)	1.54 (1.54)	0.39 (0.39)
FIT 150	4.4 (4.4)	97.2 (97.2)	0.59 (0.58)	1.78 (1.82)	0.40 (0.40)
FIT 100	5.3 (5.3)	96.8 (96.8)	0.83 (0.80)	1.98 (2.01)	0.42 (0.42)
FIT 75	6.4 (6.4)	96.3 (96.3)	0.99 (1.02)	2.30 (2.27)	0.45 (0.45)
FIT 50	8.4 (8.4)	95.2 (95.3)	1.57 (1.54)	2.73 (2.71)	0.48 (0.48)

*Advanced adenoma was defined as adenoma ≥ 10 mm or with a histology showing either a ≥ 25% villous component or high-grade dysplasia in the trials. In the model, adenomas are classified by size only and advanced adenomas were all assumed ≥ 10 mm.

of 1 or 2 adenomas and after 3 years in case 3 or more adenomas were found. We assumed that surveillance stopped at the age of 80, the oldest stop age for screening.

Attendance

We simulated the strategies assuming both 100% attendance (for gFOBT, FIT, diagnostic and surveillance colonoscopies) and observed attendance (gFOBT 50%, FIT 60%, diagnostic colonoscopies 85%).[6, 7] Attendance to surveillance colonoscopies was assumed 80% in the observed attendance scenario.[18] Based on gFOBT trial observations, we assumed that 10% of the individuals never attended FOBT screening [19] and had a higher risk for CRC than the general population (RR=1.15).[1] The remainder attended at least one round. Of the individuals that attended in a certain screening round, 80% attended again in the subsequent screening round.[20]

Costs

We included screening and treatment costs (Table 3). Organisational costs for FOBT screening were based on current expenses in the Dutch cervical screen program, adjusted for differences

Table 3: Model assumptions of the baseline and sensitivity analyses.

Variable	Baseline analysis		Sensitivity analyses	
Quality of life loss				
Colonoscopy	-		1 day per colonoscopy	
CRC treatment* (1-utility per year in treatment)	-		Initial treatment 31: Stage I: 0.26 Stage II: 0.3 Stage III: 0.4 Stage IV: 0.75 Continuous care 32: 0.15 Terminal care death by CRC: 0.75 Terminal care death by other cause: 0.35	
Correlation FOBT results	-		74% of the large adenomas (>9 mm) that are not detected, will not be detected in a next screening round 24	
			Low value	High value
Fatal complications after colonoscopy	1 per 10,000 colonoscopies		No fatal complications	1 per 1,000 colonoscopies with polypectomy, 1 per 10,000 colonosocpies without
FOBT costs				
	gFOBT	FIT		
Costs per invitation (organisational costs and test kit)	€14.05	€14.85	50%	200%
Costs per attendee (personnel and material costs for analysis)	€1.90	€4.37		
			Low value	High value
Colonoscopy costs				
Without polypectomy	€303		50%	200%
With polypectomy	€393			
Costs complications after colonoscopy **	€1250		50%	200%

Table 3 continued

Variable	Baseline analysis				Sensitivity analyses	
Treatment costs *						
	Initial treatment	Continuous care	Terminal care death CRC	Terminal care death other cause		
Stage I	€12500	€340	€17500	€4400	50%	200%
Stage II	€17000	€340	€17500	€4000		
Stage III	€21000	€340	€18500	€5200		
Stage IV	€25000	€340	€25000	€14000		

** Assumed complication rate is 2.4 per 1000 colonoscopies, 0.1 per 1000 colonoscopies is assumed fatal
*CRC treatment was divided into three clinically relevant phases – initial, continuous and terminal care. The initial phase was defined as the first 12 months following diagnosis, the terminal phase was defined as the final 12 months of life, and the continuous phase was defined as all months between the initial and last year of life phases. For patients surviving less than 24 months after diagnosis, the final 12 months of observation and costs of care were then allocated first to the last year of life phase, because the content of care for patients with short survival is more similar to the last year of life phase than the initial phase. The remainder of months of observation and costs were allocated to the initial phase, with no contribution to the continuing phase

with FOBT screening. Costs for the test kits were based on prices of the manufacturer. Costs for analysis of the tests consisted of costs for material and personnel needed during the process of registration, analysis and authorisation of returned tests. Colonoscopy costs were based on an internal study at the Erasmus MC after a six months continuous monitoring (data not shown). Additional costs for polypectomy were based on additional time and polypectomy materials needed for the procedure and costs for pathology. Costs for complications after colonoscopy were based on DBC-rates (Diagnose Treatment Combination), derived from the Dutch Health Care Authority (http://ctg.bit-ic.nl/Nzatarieven/top.do).

Costs of CRC treatment were divided into three clinically relevant phases of care: initial treatment, continuous care and terminal treatment. Initial treatment costs were based on DBC-rates, except for Oxaliplatin. The costs for Oxaliplatin were derived from the Dutch Health Care Insurance Board (www.medicijnkosten.nl). We assumed that during the continuous care phase, individuals followed the Dutch guidelines (www.oncoline.nl) and costs for periodic control were based on DBC-rates. Terminal treatment costs for patients that ultimately died of CRC were based on a last year of life analysis and were estimated at €19700.[21] We assumed that these costs increase with stage, as observed for US patients.[22, 23] Dutch terminal care costs for individuals that die of CRC were approximately 40% of the US costs. We assumed that terminal care costs of CRC patients that did not die from the disease were also 40% of the US costs.

Cost-effectiveness analysis

We used MISCAN-Colon to estimate costs and number of life-years gained for all strategies with both FOBTs compared to the situation without screening. Costs and life-years gained were discounted by 3%. Strategies that were more costly and less effective than one or more other strategies were ruled out by simple dominance. Strategies that were more costly and less effective than a mix of other strategies were ruled out by extended dominance. The remaining strategies are known as efficient. The incremental cost-effectiveness ratio (ICER) of an efficient strategy was determined compared to the next less expensive option. On a plot of costs vs. life-years gained, the line that connects the efficient strategies is called the efficient frontier, and all dominated strategies lie below this line.

Sensitivity analysis

We performed 12 sensitivity analyses on 7 parameters (Table 3). We adjusted for reduced quality of life due to screening as well as CRC treatment. Correlated FOBT results were assumed because lesions that did not bleed in the first round may have a higher than average probability of not bleeding in a next screening round too. We used the results of a population based screening program in Italy to estimate the correlation between false negative FIT results for cancers and advanced adenomas in subsequent screening rounds.[24] Low and high values were evaluated for fatal complications as well as costs.

RESULTS

Cost-effectiveness analysis

At all cost levels, FIT with the recommended cut-off level of 100 ng/ml (FIT 100) resulted in more life-years gained than gFOBT (Figure 1). When comparing different FIT cut-off levels (Figure 2), FIT 50 resulted in even more life-years gained at the same or lower costs. Consequently, the efficient frontier consisted of FIT 50 strategies only. The higher the cut-off level used, the further the strategies lied below the efficient frontier.

The costs and life-years gained of the efficient strategies are given in Table 4 under the assumption of 100% attendance. Widening the age range or shortening the screening interval resulted in more life-years gained, but increased the costs as well. Biennial screening between ages 55 and 75 resulted in 95 life-years gained per 1000 individuals compared to no screening, at a cost of 201,000 euro. The incremental costs per life-year gained compared to the next least expensive efficient strategy (screening every 3 years between ages 55 and 73) of this strategy was 3,900 euro. Increasing the screening frequency to annual screening (between ages 55 and 75) was as expensive as widening the age range to 50 and 80 (with biennial screening), but resulted in less health benefits (110 compared to 114 life-years gained per 1000 individuals).

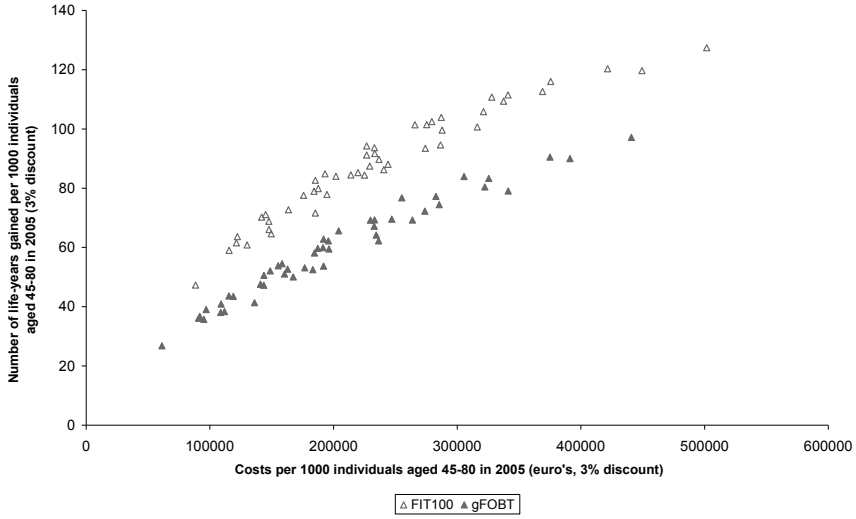

Fig 1: Costs and life-years gained (3% discount) per 1000 individuals aged 45-80 years in 2005 of strategies varying by age to begin screening, age to end screening and screen interval for gFOBT and FIT 100, with 100% attendance.

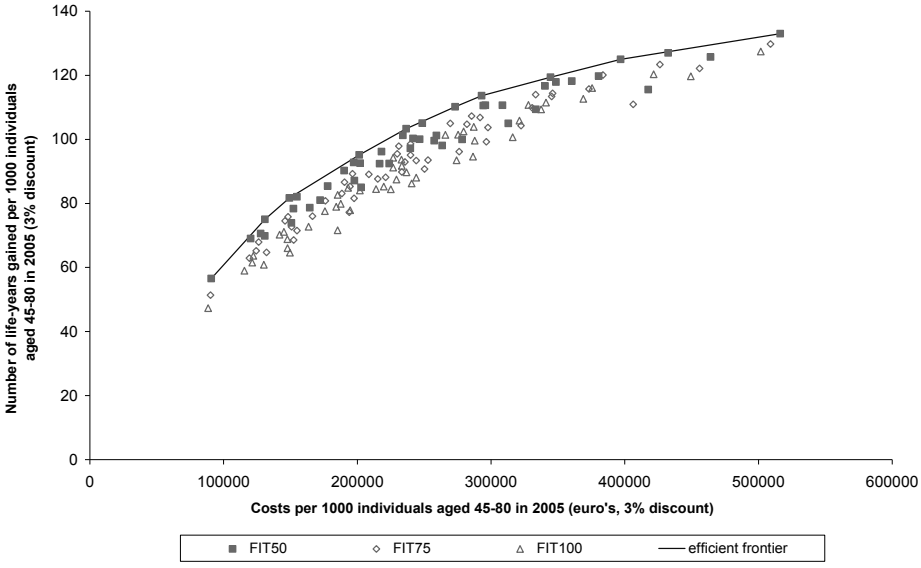

Fig 2: Costs and life-years gained (3% discount) per 1000 individuals aged 45-80 years in 2005 of strategies varying by age to begin screening, age to end screening and screen interval for FIT 50-100, with 100% attendance. The efficient strategies are connected by the efficient frontier, and are given in Table 4.

In other words, it was more cost-effective to intensify the screening program by widening the age range than by shortening the screening interval to one year. Only when a wide age range is already used, it becomes cost-effective to switch to annual screening.

Table 4: Efficient screening strategies in case of 100% attendance. All strategies use FIT with cut-off level 50 ng/ml. Costs and life-years gained per 1000 individuals aged 45-80 years in 2005 and the ICER compared to the next least expensive efficient strategy (3% discount).

begin - end age / interval / # screens	Costs	Life-years gained	ICER
60-69 / 3 / 4*	91000	57	1600
55-70 / 3 / 6	131000	75	2200
55-73 / 3 / 7*	149000	82	2800
55-75 / 2 / 11*	201000	95	3900
55-74.5 / 1.5 / 14*	237000	103	4300
55-79 / 1.5 / 17*	273000	110	5300
50-80 / 2 / 16	293000	114	5800
50-80 / 1.5 / 21	344000	119	8900
45-79.5 / 1.5 / 24	397000	125	9400
45-80 / 1 / 36*	515000	133	14900

*This strategy is both efficient for 100% and for realistic attendance

Effect of attendance rate

When accounting for observed attendance rates (50% for gFOBT, 60% for FIT and 80% for diagnostic colonoscopy), FIT 50 remained more cost-effective than gFOBT or FIT at higher cut-off levels. Costs and life-years gained decreased due to the non-attendees, while the incremental cost-effectiveness remained similar (Table 5). Based on the attendance rates observed in the trials, the expected costs and effects of biennial screening between ages 55 and 75 were 180000 euro and 68 life-years gained per 1000 individuals compared to no screening. Compared to the situation with full attendance, shorter intervals between the screening rounds became efficient when we accounted for observed attendance rates. The shorter screening intervals compensated the screening intervals of individuals that attended some but not every screening round. For example, annual screening between ages 50 and 80 was efficient now with an

Table 5: Efficient screening strategies in case of observed attendance**. All strategies use FIT with cut-off level 50 ng/ml. Costs and life-years gained per 1000 individuals aged 45-80 years in 2005 and ICER compared to the next least expensive efficient strategy (3% discount).

begin - end age / interval / # screens	Costs	Life-years gained	ICER
60-69 / 3 / 4*	76000	35	2100
60-70 / 2 / 6	106000	47	2600
55-73 / 3 / 7*	127000	53	3400
55-69 / 2 / 8	138000	56	3400
55-75 / 2 / 11*	180000	68	3600
55-74.5 / 1.5 / 14*	215000	77	4100
55-79 / 1.5 / 17*	252000	84	4900
55-80 / 1 / 26	337000	95	7700
50-80 / 1 / 31	415000	104	8400
45-80 / 1 /36*	493000	109	16100

*This strategy is both efficient for 100% and for realistic attendance

**Realistic attendance rates: 60% for FIT, 85% for diagnostic colonoscopy and 80% for surveillance colonoscopy

ICER of 8400 euro per life-year gained, while biennial screening between ages 50 and 80 was not efficient anymore.

Sensitivity analyses

The optimal cut-off level of 50 ng/ml for FIT was very robust for alternative model assumptions. Only if colonoscopy costs doubled, higher cut-off levels became efficient next to the 50 ng/ml cut-off. Biennial screening starting at age 50 or 55 and stopping at age 75 or 80 was an efficient strategy in 9 of the 12 analyses. Considering all sensitivity analyses for which biennial screening from 50/55 to 75/80 was efficient, the ICER was 10800 euro per life-year saved at most (in case of doubled cost for colonoscopy). The highest ICER value for annual screening between ages 45 and 80 was 26600 euro per life-year gained, again when costs for colonoscopy were doubled.

DISCUSSION

Our study shows that FIT screening with OC-Sensor micro is more cost-effective than gFOBT screening with Hemoccult II. Within the range analysed (50-200 ng/ml), the optimal cut-off level was 50 ng/ml. This outcome appeared very robust in the sensitivity analyses. A 50 ng/ml cut-off value is lower than the 100 ng/ml that is recommended by the manufacturer.

The number of strategies included in this analysis was limited in two ways. First of all, we did not analyse the cost-effectiveness of cut-off levels below 50 ng/ml. Observations from a cut-off below 50 ng/ml were not available because individuals with a FIT result below 50 ng/ml were not referred to colonoscopy in the trials we used. This was based on the fact that 50 ng/ml is the lower limit of test reliability. Lowering the cut-off level by definition increases the proportion of individuals referred to colonoscopy. In the hypothetical situation of screening with a cut-off of 0 ng/ml, all individuals would be invited for a colonoscopy, getting a repeat colonoscopy after 10 years if nothing was found. Therefore, the favourable result for low cut-off levels could be a result of the favourable cost-effectiveness of 10-yearly screening in our model. However, a 10-yearly colonoscopy strategy was not a cost-effective alternative compared to FIT 50 in our simulations. We also limited the number of screenings in our analysis. Even though the ICERs of the screening strategies included were well below 20000 euro per life-year gained, we did not include more intensive screening strategies (wider age ranges or shorter screening intervals), as they strongly increase the need for colonoscopy and colonoscopy capacity is limited in the Netherlands.[25] In those situations where colonoscopy capacity is unlimited, more intensive screening strategies than included in this analysis could be considered.

Other investigators came to similar results and conclusions with regard to the optimal cut-off level of FIT. In Italy, the recommendation was not to increase the cut-off level above 100 ng/ml, while lower cut-off levels were not analysed.[26] In a study in Taiwan, individuals with a test result below 100 ng/ml were followed up for two years, and sensitivity was estimated for

various cut-off levels based on interval cancers.[27] The authors concluded that 110 ng/ml was the optimal cut-off level. However, the estimated costs were lowest at a cut-off value of 40 ng/ml, while the estimated number of life-years gained decreased from 40 ng/ml to higher cut-off levels (see Figure 4a in the study by Chen [27]). The 40 ng/ml cut-off was therefore to be preferred to higher cut-off values, which is close to our finding. Some studies came to different conclusions due to the use of different optimisation criteria. In a Japanese study, workers were offered colonoscopy above a cut-off level of 50 ng/ml.[28] The authors recommend a cut-off level of 200 ng/ml based on levelling off of the ROC-curve and minimal costs per CRC case detected in one screening round. In that analysis, only screening costs and no savings of treatment costs were taken into account. Including potential savings resulting from prevented cancers would lead to a lower optimal cut-off level. Other studies based on the same data we used recommended a cut-off level of 75 ng/ml.[6, 16] In these studies, burden from and a limited capacity of colonoscopy were reasons to use the criteria that no more than two individuals need to undergo colonoscopy to detect one individual with advanced neoplasia.

The optimal cut-off level for FIT remained 50 ng/ml when taking observed attendance rates into account (50 % for gFOBT, 60% for FIT, 85% for colonoscopy after a positive FOBT). In this scenario, some of the individuals do not attend all screening rounds. As a consequence, shorter intervals between screening rounds become somewhat more cost-effective to compensate for the fact that some individuals skip a round every now and then. The shorter intervals are not necessarily optimal for individuals that do attend to every screening round. For that reason we considered 100% attendance, identifying the strategies that are optimal for individuals that follow the recommendations. This is justified because the cost-effectiveness level appeared to be very similar in both scenarios.

gFOBT is currently used in several European screening programs because of its potential to substantially reduce mortality from CRC [1-3] and its acceptable cost-effectiveness.[8] However, the sensitivity of FIT is higher than the sensitivity of gFOBT, in some studies even with a better or equal specificity.[29, 30] This was confirmed by the combined results from the Dutch trials [6, 7, 16], in which FIT 250 produced the same false positivity rate (no advanced neoplasia detected during follow-up colonoscopy) as gFOBT, while FIT 250 detected almost twice as many cases with advanced neoplasia. Regarding the unit costs, although the actual test material is more expensive for FIT than for gFOBT, personnel costs of FIT are reduced by the ease of automated handling of large volumes of FIT tests, whereas gFOBT cards have to be handled and read separately by hand. When these effects were measured in the Dutch trials, total costs for both tests appeared not to differ as much as often assumed in cost-effectiveness analyses. Given the better test performance and the limited difference in costs, it is not surprising that the effectiveness and cost-effectiveness of FIT screening are even better than the (cost)-effectiveness of gFOBT screening. The higher attendance to FIT screening further increases the additional effectiveness of FIT compared to gFOBT. Based on our results, changing from gFOBT to FIT 50 in a biennial screening program for individuals aged between 55 and 75 would increase the

number of life-years gained by screening with 130%, at an incremental cost of 1000 euro per life-year gained. Even when changing to the suboptimal FIT 100 would double the number of life-years gained compared to gFOBT screening, at an incremental cost of only 1300 euro per life-year gained.

In conclusion, this analysis strongly supports the use of FIT for future population-based CRC screening programs based on faecal occult blood testing, and to do so with a relatively low cut-off value for colonoscopy referral.

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Chapter 10

General discussion and conclusion

FAECAL OCCULT BLOOD TESTING

Main findings

The guaiac-based faecal occult blood test (gFOBT) is the most commonly used stool blood test for CRC screening and the only CRC screening test for which there is evidence of CRC-related mortality reduction from prospective randomised controlled trials (RCT).[1-4] Guaiac-based FOBT is lacking specificity as it cannot differentiate between human blood and animal blood derived from the diet. The introduction of the faecal immunochemical test (FIT) has considerably improved the detection of human occult blood in faeces by using an antibody (immunoglobulin) specific to human (haemo)globin. FIT can detect blood at lower concentrations than gFOBT, and is significantly more specific as FIT is not subject to interference from dietary blood and upper gastrointestinal blood loss.[5] Furthermore, FIT samples can be analysed automatically which has important advantages for reproducibility, quality control, capacity, and costs.[6, 7]

We demonstrated a 12% higher participation rate to FIT (62%) than gFOBT (50%) screening. A previous study suggested that dietary restrictions required for gFOBT screening were responsible for a lower uptake.[8] In this thesis we show that gFOBT screening performed without dietary restrictions still resulted in a lower uptake than FIT screening **(chapter 2)**. The less demanding sampling method for FIT (swab vs. the conventional card used for gFOBT) and the sampling from a single instead of multiple consecutive bowel movements seem likely explanations for this difference in participation rate.[9]

Limited data on experienced test burden of gFOBT and FIT screening are available.[10-12] To determine the actual experienced burden of both FOBTs, we administered a questionnaire to a random sample of participants to gFOBT and FIT screening **(chapter 5)**. Significantly less FIT than gFOBT screenees experienced discomfort during faecal collection and test performance. Again, the sampling method and the number of faecal samples required may explain this difference in discomfort.[9]

Several studies demonstrated more favourable test characteristics of FIT compared to gFOBT screening.[13-17] In a randomised trial we demonstrated that the FIT (OC-Sensor micro) with a cut-off value of 100ng/ml detected significantly more advanced neoplasia than the gFOBT (Hemoccult II), whereas the number of false negatives was similar for both tests **(chapter 2)**. We used a quantitative FIT, which allows determination of an optimal cut-off level for a nationwide screening programme based on colonoscopy capacity and the intended detection rate in the screened population. We therefore determined the optimal cut-off value in a second study described in **chapter 3**. A cut-off value of 75ng haemoglobin/ml provided an adequate positivity rate and an acceptable trade-off between detection rate and number needed to scope (NNscope) to find one screenee with an advanced neoplasia. One could argue to use a higher cut-off value for women as the detection rate and NNscope was less favourable in women than in men given the lower prevalence of advanced neoplasia in women.

In Europe, screening programmes are mostly covered by local or national governments. Therefore, the actual decision about the implementation of a CRC screening programme should preferably also be based on its cost-effectiveness. Biennial gFOBT screening has demonstrated to be cost-effective.[18, 19] Previously, a French study estimated the additional costs of using biennial FIT in stead of a biennial gFOBT at 3000 euro per life-year gained.[20] We performed the first cost-effectiveness analysis comparing gFOBT and FIT based on randomised data **(chapter 9)**. For this study we used the MISCAN-Colon micro-simulation model to estimate costs and effects of different screening strategies comparing gFOBT (hemoccult II) with one sample FIT (OC-Sensor micro) at cut-off levels of 50, 75, 100, 150 and 200ng Hb/ml. Screening strategies in the model varied with respect to age range and screening interval. The costs per invitation were similar for both tests, as the FIT we used can be analysed automatically which reduces personnel need and thus lowers the costs per test. FIT screening was estimated to be more cost-effective than gFOBT screening based on the better performance and similar costs. The optimal cut-off level was 50ng/ml. Biennial FIT (cut-off 50ng/ml) screening between ages 55 and 75 resulted in an incremental cost-effectiveness ratio of 3900 euro per life-year gained. Extending the programme by a wider age range (50-80 years) was more cost-effective than shortening the screening interval (annual). However, randomised trials on the optimal screening interval are not available, and for the model we therefore made assumptions based on gFOBT trial observations.

Conclusions and further research

Several countries have a nation-wide screening programme mainly based on gFOBT, since this is the only available test with a proven mortality reduction.[1-4] Although prospective RCTs on FIT screening are lacking, we conclude based on this thesis that FIT should be preferred over gFOBT screening. FIT has superior participation and detection rates, lower test burden, and higher cost-efficacy. The results are based on Dutch data, but will also be applicable to other countries in the Western World. A biennial screening programme was estimated to be most cost-effective. However, evidence from randomised studies investigating the optimal time interval for detecting advanced colorectal neoplasia in a screening programme by FIT are eagerly awaited.

Our results are based on the one sample FIT. Further investigation on the optimal number of samples per round is required. Recently, a French study reported a similar performance on the relative ROC curves (in reference to G-FOBT) of a one sample FIT and a two-sample FIT with a referral for TC if at least one sample was positive. The most gain in sensitivity and specificity was obtained with a two-sample FIT when the mean of measured Hb levels was used for TC referral.[21] This finding needs to be further explored in cost-effectiveness analyses.

FLEXIBLE SIGMOIDOSCOPY

Main findings

Sigmoidoscopy has shown to be a feasible screening tool.[22-25] The main drawback for introducing a nation-wide FS screening programme is the low participation rate. In agreement with data from other countries [22, 25-28], we demonstrated that 32% of eligible average risk subjects was willing to undergo a FS **(chapter 2)**. However, a Norwegian study reported significantly higher uptake levels (65%). Research has consistently shown that expected pain or discomfort is one of the most important reasons for declining the endoscopic screening offer.[29, 30] An Italian study demonstrated that 23% of non-participants of a FS screening programme reported anticipated pain, discomfort, or injury as the main reason for refusing FS screening.[31] Those barriers may be overcome by offering non-participants an alternative screening test, for example FIT. We therefore invited non-participants of our FS screening programme for FIT screening. In total 25% of non-participants to FS screening was willing to undergo a non-invasive and less burdensome FIT test. Our results validate the finding of Senore et al. in a true experimental setting **(chapter 4)**.[31] Thus, the FS itself seems to be a strong barrier for participation.

To determine which specific aspects of screening tests mainly determine the preference for a screening test, we performed an unlabelled discrete choice experiment (DCE). Our results confirmed that expected pain is an important determinant of preference for a screening strategy in screening naïve individuals and significantly influences the expected participation rate based on our model **(chapter 7)**. Furthermore, we demonstrated that pain significantly less influenced preferences among those with endoscopy experience. This suggests that pain actually experienced during endoscopic screening is not as severe as expected beforehand **(chapter 7)**.

We determined level of embarrassment, discomfort, and pain among participants to FS screening **(chapter 6)**. As suggested before, we and others found only a small proportion of screenees reporting severe embarrassment, discomfort or pain during the procedure.[22, 27, 32-34] Even more important, only 8% of subjects was not willing to return for a successive FS screening round and only 2% would not recommend others to undergo FS screening. FS screening is thus an acceptable screening method among participants, which has very important implications for the implementation of a nation-wide screening programme, since FS screening must be repeated five or ten-yearly to be effective.[35-37] Furthermore, participants will share their (positive) experience with FS screening with other potential screenees. This may improve uptake in successive cohorts.

The low participation rate to more invasive screening tests, like FS, might also be explained by the lack of information on a more substantial risk reduction on CRC-related mortality than seen with the non-invasive FOBTs. Screenees in our and other large population-based trials were however not specifically informed on test efficacy **(chapter 2)**.[22, 24-28] We performed a labelled DCE, in which respondents had to choose between FOBT, FS and total colonoscopy

(TC) with test-specific risk reduction on CRC-related mortality **(chapter 6)**. The predicted uptake of FS and TC screening based on our model was significantly higher than uptake of FOBT screening, given realistic levels of CRC-related mortality reduction. Our findings are further underlined by a Swiss study, in which the majority (75%) of all screenees chose to undergo a TC, and only a small proportion (25%) preferred FOBT or FS screening after they were informed about the efficacy of the three screening tests.[38] We therefore believe that increasing awareness on the efficacy of FS screening will enhance uptake, prevent unrealistic expectations, and optimise informed choice. Uptake of FS screening in the Netherlands may thus be higher in future programmes if invitees will be informed on efficacy of FS screening. The effectiveness of FS screening has been evaluated in case-control studies [39-41], and recently results of a RCT have been published.[42] The mortality reduction in this trial was 59% among attendees.[42] The results of three large RCT are still being awaited.[22, 23, 25] In this thesis we describe the detection rate (DR) of advanced neoplasia as surrogate end-point for the effectiveness of FS screening **(chapter 2)**. The DR of advanced neoplasia (8.0%) in the FS arm was high compared to other studies (3.6-5.2%).[22, 24, 26-28] The inclusion of an older age group (50-74 years) with a higher prevalence of advanced neoplasia partly explained this difference. In addition, we aimed to examined the colon until the splenic flexure, which will ultimately lead to a higher DR, while other studies reached for the transition from sigmoid to descending colon as anatomic extent of FS.[22, 25, 27]

Recently, a Canadian case-control study demonstrated that colonoscopy is associated with a reduction in CRC-related mortality rates, but primarily for left-sided cancer.[43] This study is limited by the retrospective design, the lack of information on the indication for the colonoscopy, and the use of billing codes instead of actual endoscopy reports. Nevertheless, the results are supported by two population-based cohort studies which reported similar trends as the occurrence of CRC [44] and advanced neoplasia [45] was decreased in the left and not the right sided colon ten year after a screening colonoscopy. Assumptions for the lack of protective effect in the right colon are: (i) reduced quality of colonoscopy (e.g. caecal intubation, adenoma detection rate, withdrawal time) as in those population-based studies colonoscopies have been performed by others than a gastroenterologist (surgeons, general practitioners); (ii) increased prevalence of flat or sessile lesions in the right colon, which are more likely to be missed; and (iii) adenoma in the right colon may develop through a different, possibly fast-growing pathway (e.g. microsatellite instability). Although prospective population-based trails are required to confirm these findings, we postulate that a high quality FS until the splenic flexure and referral of high risk subjects for TC might be a reasonable alternative for TC screening in the era of limited colonoscopy capacity.[46] The efficacy of a FS programme can be further improved by adding biennial FOBT screening, as FOBT screening has been proven to reduce CRC related mortality mainly in the right colon.[47, 48] A recent cost-effectiveness analyses based on US data demonstrated that the combination of FS and FOBT (Hemoccult II) was the most effective, cost-saving screening method. Lansdrop-Vogelaar et al. did not describe the combination of FS

and FIT. Based on our randomised trial FIT outperformed gFOBT in uptake, detection rate and cost-effectiveness **(chapter 2 and 9)**. Combining FS with FIT in stead of gFOBT will probably be more cost-effective. Until now only one small population-based study has been performed showing a 10% increase in detection rate when a FIT was added to FS screening.[49]

Conclusions and further research

FS is a feasible screening test for use in a nation-wide screening programme. For improving effectiveness of FS screening, the focus should be on higher participation rates. Invitees of a FS screening programme should be informed on the expected reduction of CRC related mortality with FS screening, as this may improve uptake and enhance informed choice. Further population-based trials using FS screening, in which subjects in the target population are informed on the effectiveness, are required. Furthermore, RCT results on FS screening to reveal the CRC-related incidence and mortality reduction are eagerly awaited.

The combination of gFOBT and FS is more cost-effective than FS alone. Guidelines recommend the combination of FS with a sensitive FOBT .[37] Based on our data a combination with FIT seems the most (cost-) effective, and should be preferred over gFOBT. However, large population based studies determining uptake and diagnostic yield of a combined FS/FIT programme are required.

GENDER DIFFERENCES IN ENDOSCOPIC CRC SCREENING

Main findings

International guidelines recommend similar screening strategies (test, interval, age to initiate screening) for men and women [35, 37, 50], despite disparity in epidemiology of CRC.[51] The question is raised whether gender-specific screening policies should be introduced.[52]

Age-specific CRC incidence and mortality rates in men are similar to women who are approximately 4–8 years older.[53] Colonoscopy studies found a considerable lower detection rate of advanced neoplasia in women than men in their sixth decade, whereas the detection rate was similar for both sexes above the age of 60.[54-56] These findings may provide a rationale for delaying initiation of CRC sceening in women.

The incidence of CRC per colon segment also varies between both sexes, as women are more likely to have a right-sided CRC.[57] A FS has been shown to predict the presence of advanced neoplasia in the proximal colon only in a minority of cases (35%).[55] In agreement with all large population-based FS studies, we found a significant larger number of advanced neoplasia in men than in women **(chapter 2)** [22, 24, 25, 27], and thus a higher number needed to screen among women. FS screening therefore seems less effective in women. However, we have to take into account that women have a longer life expectancy which may partly compensate for the fewer neoplasia found.

In **chapter 2** we demonstrated a significantly lower uptake of FS screening among women compared to men. A subsequent invitation for FIT screening resulted in a higher response among female than male FS non-participants, indicating that the test rather than the CRC screening itself was a barrier to participation **(chapter 4)**. These results are in agreement with our labelled DCE demonstrating a more negative attitude towards both FS and TC screening among women than among men **(chapter 6)**. Compared to men, women reported more fear and embarrassment to undergo a FS [58], which were the main reasons for refusing FS.[31] We conducted a questionnaire study among participants of FS screening to reveal the actual difference in experienced burden between both sexes. Our observations reflect those of other studies reporting that women were more likely to experience burden during FS, [59, 60] and were therefore less willing to return for successive screening rounds. Interestingly, experienced embarrassment was less pronounced in women who underwent a FS performed by a same-sex endoscopist.[61, 62] Nickelson et al. previously reported expected embarrassment as the most important reason for preferring a same-sex endoscopist.[58] Our results demonstrate that, in this case, the expectation reflects the actual experience **(chapter 5)**.

Conclusions and further research

Indirect evidence suggest less effectiveness of FS screening in women, based on a higher prevalence of right-sided CRC, worse prediction of advanced neoplasia in the proximal colon based on distal findings and a less favourable attendance rate. Sex-specific data of RCTs and cost-effectiveness analyses CEAs for FS screening are being awaited to decide on FS as a screening tool in women.

If the results are favourable, attempts should be made to improve attendance among women. Endoscopists should be aware of potential embarrassment, discomfort and pain in women, and should consider steps to reduce burden during FS (e.g. using sedation or a more flexible, smaller-calibre endoscope). Furthermore, a nation-wide screening programme should offer potential screenees a choice between a male or female endoscopist or directly allocate all female participants to a female endoscopist. Further research should focus on sex-specific information to reduce anticipated embarrassment and fear.

END-POINTS OF CRC SCREENING

Main findings

The detection rate of advanced adenomas is used as a surrogate end-point for the effectiveness of a screening strategy. Additionally, surveillance and screening guidelines for subjects with colorectal polyps rely on the histological characteristics of polyps removed. Concerns have been raised on the reproducibility of pathology results. In this thesis we demonstrated that pathologists show a very good inter-observer agreement for differentiating between

non-adenomatous and adenomatous polyps (kappa-value 0.88), and a moderate agreement for non-advanced and advanced adenomas (kappa-value 0.58). Our findings are in line with previous studies.[63-70] Surprisingly, pathologists with expertise in gastroenterology demonstrated similar inter-observer variability in the classification of advanced and non-advanced adenoma as other pathologists (**chapter 8**).[63-70]

Conclusions and further research

The moderate inter-observer agreement between general and expert pathologists in the field of gastroenterology for advanced and non-advanced adenoma has serious implications for evaluation of the effectiveness of screening strategies and for risk stratification of patients with neoplasia removed. An adenoma with advanced characteristics remains an important determinant of cancer risk. We therefore recommend focusing on education and continuous quality improvement efforts with regard to interpretation of colon neoplasia. A consensus meeting on interpretation of colon neoplasia prior to implementation of a nation-wide screening programme seems warranted. Further research on more reliable markers for predictability of recurrence of advanced neoplasia is required.

ROLE OF THE GENERAL PRACTITIONER IN CRC SCREENING

Main findings

The role of the general practitioner (GP) is of paramount importance for a nation-wide screening programme, especially in the Netherlands where the GP is the central stakeholder of health care. GP's recommendation on CRC screening is a major predictor for attending CRC screening.[30, 31, 71, 72] Before implementing a nation-wide screening programme, it is of vital importance that the majority of GP's have a positive attitude towards screening. Furthermore, GP's should achieve adequate information on all aspects of CRC screening.

On the other hand, involvement of the GP in the invitation process is questionable, as two randomised population-based trial did not demonstrate any benefit of personalised invitation by the GP.[9, 28, 73] This should therefore not be recommended for a nation-wide screening programme. In addition, a central invitation system is more opportune and will not overlook subjects in the target population without a GP.[74]

Involving GPs in the process of informing screenees on a positive test result and the subsequent referral considerably increases uptake of a follow-up TC. In this thesis, nearly all positive screenees underwent a colonoscopy (97%) (**chapter 2**). This is considerably higher than observed in the study of Van Rossum et al (83%), which had a similar design and was also conducted in the Netherlands.[16] We, other than van Rossum et al., put the GP in charge of informing the screenee on the positive test result and further handling the referral of the

screenee. Furthermore, in our study GPs could refer positive screenees to all hospitals in the region, while in the study by Van Rossum et al. all TC were performed in the university hospital.

Conclusions and further research

The GP has an important role in a nation-wide screening programme to inform subjects in the target population on CRC screening and in the referral process of subjects with a positive screen.

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Summary

Samenvatting

SUMMARY

Chapter 1 provides an overview of the current knowledge on epidemiology of and screening strategies for colorectal cancer (CRC). Furthermore, the general aims and outline of the thesis are described in this chapter.

In **chapter 2** a randomised trial comparing uptake and detection rate of guaiac-based faecal occult blood test (gFOBT), faecal immunochemical test (FIT), and flexible sigmoidoscopy (FS) screening in a Dutch average-risk screening naïve population (n=15 011) is described. Faecal immunochemical test at a cut-off value of 100ng Hb/ml provided a higher uptake (62% vs. 50%, p<0.001) and detection rate of advanced neoplasia (2.4% vs. 1.1%, p<0.001) than gFOBT screening. Based on these findings FIT is preferred over gFOBT for population-based screening. Uptake of FS screening (32%) was significantly lower than for both FOBTs. Despite this lower uptake, FS screening demonstrated a higher diagnostic yield per 100 invitees than both FOBTs (gFOBT 0.6; FIT 1.5; FS 2.4 advanced neoplasia/invitee p<0.001).

The FIT (OC-Sensor micro) provides quantitative test results allowing for determination of an optimal cut-off value for a nation-wide screening programme based on colonoscopy capacity and the intended detection rate in the screened population. **Chapter 3** describes the characteristics of FIT at different cut-offs in the range of 50-200ng Hb/ml and provides a random comparison with gFOBT screening. FIT was a more effective screening test than gFOBT within the range of tested cut-off values. A cut-off value of 75ng Hb/ml provided an adequate positivity rate (5.8%) and an acceptable trade-off between positive predictive value (PPV) (49% CI 42-57%) and detection rate of advanced neoplasia (2.7%; CI 2.2-3.3%). PPV (65% vs. 42%; p<0.001) and detection rate (4.1% vs. 1.7%; p<0.001) of advanced neoplasia in FIT screening were significantly higher in men than in women. A different cut-off level for men and women to achieve a similar PPV may therefore be considered.

Uptake of FS screening generally remains low, as described in chapter 2. In **chapter 4** we therefore determined uptake of FIT screening among non-participants of FS screening. In total 25% (CI 24-26%) of the non-participants of FS screening did attended FIT screening. The overall participation rate of the two-stage recruitment for FS and FIT screening was 45% (CI 44-46%). However, the attendance remains lower than for primary FIT screening (62%). Women in the target population were more likely to attend FIT than FS screening (p<0.001).

Perceived burden of a screening test is an important determinant of acceptance of a population-based screening programme. In **chapter 5** experienced burden of gFOBT, FIT and FS screening was determined among participants. A significant larger proportion of gFOBT than FIT screenees reported test-related burden (gFOBT: 2.5%; FIT: 1.4%; p=0.05). Both FOBTs were reported to be less burdensome than FS screening (12.9%, p<0.001). Furthermore, FS-related burden was more frequently reported by women than by men (18.2% vs. 7.7%; p<0.001). Our data demonstrate that a same-sex endoscopist may reduce the level of perceived embarrassment in women, whereas no differences in pain or discomfort were found. A nation-wide

FS screening programme should therefore offer women in the target population a choice between a female and male endoscopist. All three screening tests seem to be acceptable for population-based screening as the majority was willing to attend successive screening rounds (gFOBT: 94.1%; FIT: 94.0%; FS: 83.8%). This positive experience with CRC screening may affect uptake of subsequent screening rounds.

International guidelines recommend screening with any test, as insufficient evidence is available to prefer one screening test over the other. Individual preferences therefore play an important role in the choice for a screening strategy. In **chapter 6 and 7** we describe two studies to determine individuals' preferences for and to predict uptake of CRC screening programmes with various screening tests. A discrete choice experiment (DCE) questionnaire was conducted among screening naïve and previously screened subjects aged 50-74. DCEs can measure individuals' preferences for health care interventions. The DCE assumes that the individual preference for a test is determined by the characteristics of a test. In **chapter 6** we performed a labeled DCE. In a labelled design the specific screening test is mentioned in each choice option (FOBT, FS, TC), while in an unlabelled design (chapter 7) the screening test is presented as 'screening test 'A', 'B' or 'C', and is further described by certain characteristics that are presented in the choice set. Type of screening test, screening interval, and risk reduction of CRC related mortality influenced subjects' preferences (all $p<0.05$). Screening-naïve and previously screened subjects equally preferred five-yearly FS and ten-yearly total colonoscopy (TC) ($p=0.24$; $p=0.11$), but favoured both strategies to annual FOBT screening (all p-values <0.001) if, based on the literature, realistic risk reduction of CRC related mortality was applied.

Chapter 7 describes how procedural characteristics of various CRC screening methods determine preferences for participation, and how individuals weigh these against the expected health benefits from CRC screening. In this study an unlabelled DCE was used. The type of bowel preparation, risk reduction of CRC-related mortality and screening interval mainly determined the preferences for a screening strategy. Both DCEs demonstrate that the expected risk reduction of CRC mortality dominated preferences for a screening strategy. Subjects in the target population should therefore be informed on risk reduction by different screening strategies to prevent unrealistic expectations and to optimise informed choice.

The histopathological diagnosis is crucial for management of patients in a screening or surveillance programme for CRC. Furthermore, the definition of advanced adenoma is increasingly used as a primary end-point in screening trials. In **chapter 8** we determined the inter-observer variation in histopathological diagnosis of colorectal polyps derived from a CRC screening programme. Furthermore, inter-observer variation was assessed between general and expert gastrointestinal pathologists, and between expert gastrointestinal pathologists. The inter-observer agreement was very good for differentiating between non-adenomas and adenomas (kappa: 0.88; CI: 0.83-0.94), but only moderate for distinguishing non-advanced from advanced adenomas (kappa: 0.58; CI: 0.48–0.68). The inter-observer variation in the interpreta-

tion of colorectal polyps was similar between a general and an expert pathologist as between two expert pathologists.

A cost-effectiveness analysis mainly determines the governmental decision on a nation-wide screening programme. **Chapter 9** describes the cost-effectiveness of both gFOBT and FIT screening at different cut-off levels based on a random comparison of both tests in an average-risk population. In this chapter the validated MISCAN-Colon micro-simulation model was used to estimate costs and effects of different screening strategies. FIT screening at a cut-off level of 50 ng Hb/ml was most cost-effective. Biennial FIT screening between ages 55-74 resulted in an incremental cost-effectiveness ratio of 3900 euro per life-year gained. Adjusting the age range to ages 50-80 was more cost-effective than adjusting the screening interval to annual screening (5800 versus 14900 euro per life-year gained).

The main findings of this thesis and directions for future research are discussed in **chapter 10**.

SAMENVATTING

In **hoofdstuk 1** wordt een overzicht gegeven van de huidige kennis over de epidemiologie van darmkanker en screening naar darmkanker. Tevens worden de algemene doelstellingen van dit proefschrift beschreven.

In **hoofdstuk 2** wordt een gerandomiseerde studie beschreven waarin de guaiac feces occult bloed test (gFOBT), immunochemische feces occult bloed test (FIT) en de sigmoidoscopie (FS) met elkaar worden vergeleken op basis van opkomst en diagnostische opbrengst in mensen met een gemiddeld risico op darmkanker (n=15011). In deze studie werd voor de FIT een verwijsdrempel van 100ng hemoglobine (Hb)/ml gebruikt. In vergelijking met gFOBT resulteerde FIT screening niet alleen in een hogere opkomst (62% vs. 50%, p<0.001), maar detecteerde tevens een groter aantal hoogrisico neoplasieën (advanced neoplasia) (2.4% vs. 1.1%, p<0.001). Deze studie toont aan, dat FIT de voorkeur verdient boven gFOBT screening. De opkomst voor FS screening was significant lager dan voor beide FOBTs (32%). Desondanks was de diagnostische opbrengst per uitgenodigde persoon hoger voor FS dan voor beide FOBTs, doordat FS screening significant meer hoogrisico neoplasieën detecteerde (gFOBT 0.6; FIT 1.5; FS 2.4 hoogrisico neoplasieën / uitgenodigde persoon p<0.001).

De FIT (OC-Sensor micro) is een kwantitatieve test. Hierdoor is het mogelijk de verwijsdrempel te verschuiven en de afkapwaarde te bepalen, waarbij de testprestaties het meest optimaal zijn. De colonoscopie capaciteit en de gewenste diagnostische opbrengst spelen bij de keuze voor een afkapwaarde een belangrijke rol. **Hoofdstuk 3** beschrijft de testkenmerken van de verschillende afkapwaarden variërend van 50-200 ng Hb/ml in een gerandomiseerde vergelijking met de gFOBT. FIT was een effectievere screeningsmethode dan de gFOBT binnen het bereik van de geteste afkapwaarden. Een afkapwaarde van 75ng Hb/ml (FIT^{75}) resulteerde in een aanvaardbaar aantal mensen met een positieve test (5.8%). Met de FIT^{75} werden twee en een half maal zoveel hoogrisico neoplasieën (2.7% vs. 1.1%) gevonden dan met de gFOBT, terwijl de positief voorspellende waarde (PVW) voor hoogrisico neoplasieën vergelijkbaar was voor beide testen (49% vs. 45%). Op basis van deze resultaten wordt een afkapwaarde van 75ng Hb/ml geadviseerd. De PVW (65% vs. 42%; p<0.001) en het aantal gedetecteerde hoogrisico neoplasieen (4.1% vs. 1.7%; p<0.001) was significant hoger in mannen dan in vrouwen. Verschillende afkapwaarden voor FIT screening in mannen en vrouwen op basis van een vergelijkbare PVW kan derhalve worden overwogen.

Uit hoofdstuk 2 blijkt, dat de opkomst bij FS screening beduidend lager is dan bij FOBT screening. In **hoofdstuk 4** wordt de opkomst bij FIT screening bestudeerd in een groep niet-deelnemers aan FS screening. De uitnodiging werd door 25% (CI 24-26%) van de niet-deelnemers geaccepteerd. De totale opkomst bij de gecombineerde uitnodiging voor FS en FIT screening was 45% (CI 44-46%). Dit opkomstpercentage was echter lager dan beschreven voor primair FIT screening (hoofdstuk 2, 62%). Vrouwen in de doelgroep waren meer bereid om FIT dan FS screening te ondergaan (p<0.001).

De mate waarin een screeningtest als belastend wordt ervaren, is bepalend voor de acceptatie van en deelname aan vervolgronden van een screeningstest. In **hoofdstuk 5** wordt de test belasting van gFOBT, FIT en FS screening onderzocht onder deelnemers. Deelnemers aan gFOBT rapporteerden vaker enige mate van testbelasting dan deelnemers aan FIT screening (gFOBT 2.5%; FIT 1.4%; p=0.05). Beide ontlastingstesten werden als minder belastend ervaren dan de FS (12.9%, p<0.001). De meerderheid van de deelnemers was bereid om deel te nemen aan een vervolgronde met dezelfde test (gFOBT: 94.1%; FIT: 94.0%; FS: 83.8%). Deze positieve ervaring met screening voor darmkanker heeft zeer waarschijnlijk een positieve invloed op de opkomst voor vervolgronden. Verder wordt in hoofdstuk 5 beschreven, dat een groter aantal vrouwen dan mannen de FS als belastend ervoeren (18.2% vs. 7.7%; p<0.001). Uit onze analyses blijkt dat vooral de mate van schaamte, die bijdraagt aan de ervaren belasting tijdens een onderzoek, gereduceerd kan worden wanneer een vrouw gescopieerd wordt door een vrouwelijke endoscopist. Deze data benadrukken het belang van het aanbieden van een keuze voor een vrouwelijke endoscopist aan vrouwen in de doelgroep voor darmkanker screening middels FS.

Internationale richtlijnen bevelen al langere tijd screening voor darmkanker aan. Daar er onvoldoende bewijs is om een test boven een andere test te verkiezen, wordt screening met één van de bestaande testen aanbevolen. Individuele preferenties spelen dus een belangrijke rol in de keuze voor een screeningstest. In hoofdstuk 6 en 7 hebben we de individuele preferenties voor de verschillende screeningstesten onderzocht door middel van een discrete keuze experiment (DCE) uitgevoerd onder mensen tussen de 50-74 jaar met en zonder ervaring met darmkanker screening. Bij een DCE wordt aangenomen dat individuele preferenties voor een test bepaald worden door de verschillende testeigenschappen. In **hoofdstuk 6** wordt een gelabeld DCE beschreven. Een gelabeld DCE neemt ook de test zelf mee in de keuze, die wordt voorgelegd (FOBT, FS, TC). Terwijl bij een niet-gelabeld DCE de test wordt beschreven aan de hand van de testeigenschappen, die worden weergegeven in de geschetste scenario's. In het gelabelde DCE waren de test zelf, het screeningsinterval en de verwachte risico reductie van darmkanker gerelateerde mortaliteit belangrijk voor de individuele preferenties voor een bepaalde screeningsstrategie (p<0.05). De groep met en de groep zonder ervaring met darmkanker screening hadden geen voorkeur voor vijfjaarlijks FS of tienjaarlijks screenen middels colonoscopie (p=0.24; p=0.11). Echter beide endoscopische screeningsmethoden werden verkozen boven jaarlijks screenen middels FOBT (p-waarden <0.001) indien, op basis van de literatuur, realistische getallen voor het verwachte effect op darmkanker gerelateerde mortaliteit werden toegepast. De meer gunstige risico reductie en langere screeningsinterval zijn de reden, dat mensen endoscopie screening prefereren boven een FOBT.

Hoofdstuk 7 beschrijft hoe de testeigenschappen van de verschillende screeningstesten individuele preferenties beïnvloeden en hoe individuen negatieve testeigenschappen afwegen tegen het verwachte effect op darmkanker gerelateerde mortaliteit. Voor deze studie is gebruik gemaakt van een niet-gelabeld DCE. Het type darm voorbereiding, het screeningsinterval en het verwachte effect op darmkanker gerelateerde mortaliteit bepalen hoofdzakelijk

de preferenties voor een bepaalde screeningsmethode. Beide DCEs laten zien, dat de risicoreductie op darmkanker gerelateerde mortaliteit preferenties voor een screeningsmethode domineert. Mensen in de doelgroep voor darmkanker screening moeten daarom worden geïnformeerd over het effect op de darmkanker gerelateerde mortaliteit van de verschillende screeningsmethoden om onrealistische verwachtingen te voorkomen en mensen een goed geïnformeerde keuze te laten maken.

De histologische diagnose van colorectale poliepen is van doorslaggevend belang voor darmkanker screening en surveillance programma's. Tevens wordt de aanwezigheid van een hoogrisico neoplasie in toenemende mate gebruikt als primair eindpunt in studies over darmkanker screening. In **hoofdstuk 8** beschrijven wij de interobserver variatie tussen pathologen in de beoordeling van colorectale poliepen, die zijn verwijderd tijdens darmkanker screening. De interobserver variatie werd bepaald tussen een algemeen patholoog en een patholoog met maag-, darm- en lever ziekten als aandachtsgebied (expert) en tussen twee expert pathologen. De interobserver overeenstemming was erg goed voor de differentiatie tussen niet-adenomen en adenomen (kappa 0.88; CI: 0.83-0.94), maar slechts matig voor het onderscheid tussen laag en hoogrisico adenomen (kappa 0.58; CI: 0.48–0.68). De interoberserver variatie was vergelijkbaar tussen een algemeen en een expert patholoog en twee expert pathologen.

De overheidsbeslissing over de invoering van een bevolkingsonderzoek naar darmkanker zal hoofdzakelijk worden bepaald door de kosteneffectiviteit van een screeningsmethode. In **hoofdstuk 9** wordt de kosteneffectiviteit van gFOBT en FIT screening op de verschillende afkappunten berekend door middel van het gevalideerde MISCAN-Colon micro simulatie model. FIT screening was meer kosteneffectief dan gFOBT screening. FIT was het meest kosteneffectief bij een afkapwaarde van 50 ng/ml. De incrementele kosteneffectiviteit per gewonnen levensjaar voor tweejaarlijks screenen middels FIT in de leeftijdsgoep van 55-75 jaar was 3900 euro. Het vergroten van de doelgroep (50-80 jaar) was meer kosteneffectief dan het aanpassen van het screeningsinterval (jaarlijks) (5800 versus 14900 euro per gewonnen levensjaar).

De belangrijkste bevindingen van dit proefschrift en aanwijzingen voor toekomstig onderzoek worden besproken in hoofdstuk 10.

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8. van Dam L, Hol L, Bekker-Grob EW, Steyerberg EW, Kuipers EJ, Habbema JD, Essink-Bot ML, van Leerdam ME. What determines individuals' preferences for colorectal cancer screening programmes? A discrete choice experiment. Eur J Cancer 2010;46:150-159.
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12. Hol L, de Jonge V, van Leerdam ME, van Ballegooijen M, Looman CWN, van Vuuren AJ, Reijerink JCIY, Habbema JDF, Essink-Bot ML, Kuipers EJ. Screening for colorectal cancer;

comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy. Eur J Cancer 2009: in press.
13. Hol L, de Jonge V, van Ballegooijen M, Habbema JDF, Essink-Bot ML, van Vuuren AJ, van Leerdam ME, Kuipers EJ. Screening for colorectal cancer in The Netherlands; acceptance of faecal occult blood test and flexible sigmoidoscopy screening. submitted .
14. Hol L, Kuipers EJ, van Ballegooijen M, Van Vuuren AJ, Reijerink JCIY, Habbema JDF, Van Leerdam ME. Uptake of faecal immunochemical test screenig among non-responders of a flexible sigmoidocsopy screening programme. Submitted.
15. Wilschut JA, Hol L, Dekker E, Jansen J, van Leerdam ME, Lansdorp-Vogelaar I, Kuipers EJ, Habbema JDF, van Ballegooijen M Cost-effectiveness analysis comparing a quantitative immunochemical test at different cut-off levels with a guaiac faecal occult blood test. Submitted.
16. Van Putten PG, Hol L, Van Dekken H, Van Krieken JH, Van Ballegooijen M, Kuipers EJ, Van Leerdam ME. Inter-Observer Variation In The Histological Diagnosis Of Polyps In Colorectal Cancer Screening. Submitted.

PHD PORTFOLIO SUMMARY

ORAL PRESENTATIONS

2009 What determines individuals' preferences for colorectal cancer screening tests? a discrete choice experiment.
Dutch Society of Gastroenterology. Veldhoven, the Netherlands.

Implementation of CRC screening in the Netherlands.
Regional multidisciplinary symposium: treatment of rectal carcinoma, the new guidelines. Renesse, the Netherlands.

2008 Randomized trial comparing the test characteristics of immunochemical fecal occult blood test at different cut-off levels to guaiac-based fecal occult blood test.
Dutch Society of Gastroenterology. Veldhoven, the Netherlands.

Screening for colorectal cancer in the Netherlands.
Regional symposium for general practitioners. Rotterdam, the Netherlands.

Screening for colorectal cancer; randomised controlled trial comparing two different forms of faecal occult blood testing and sigmoidoscopy.
United European Gastroenterology Week. Wien, Austria.

Screening for colorectal cancer in Europe.
4th East-West Colorectal Days, Hajdúszoboszló, Hungary.

Attendance to screening for colorectal cancer in the Netherlands; Randomized trial comparing two different forms of fecal occult blood tests and sigmoidoscopy.
Digestive Disease Week San Diego, USA.

Screening for colorectal cancer in the Netherlands; randomized trial comparing two different forms of fecal occult blood tests and sigmoidoscopy.
Dutch Society of Gastroenterology. Veldhoven, the Netherlands.

Gender differences in colorectal cancer.
Symposium for Medical students. Erasmus University, Rotterdam, the Netherlands.

2007 Implementation of screening for colorectal cancer, an update.
Regional symposium for general practitioners. Rotterdam, the Netherlands.

POSTER PRESENTATIONS

2009 Randomized trial comparing the test characteristics of Immunochemical fecal occult blood test at different cut-off levels to guaiac-based fecal occult blood test.
Digestive Disease Week, Chicago, USA.

What determines individuals' preferences for colorectal cancer screening tests? a discrete choice experiment.
Digestive Disease Week, Chicago, USA.

2008 MicroRNA expression profiling of colorectal cancer and its precancerous lesions using Lna™ Oligonucleotide arrays.
Digestive Disease Week, San Diego, USA.

Risk stratification among individuals attending population-based colorectal cancer screening in the Netherlands.
Digestive Disease Week, San Diego, USA.

Diagnostic yield of screening for colorectal cancer in the Netherlands; Randomized trial comparing two different forms of fecal occult blood testing and sigmoidoscopy.
Digestive Disease Week, San Diego, USA (poster of distinction).

MEMBERSHIPS

2008 International ColoRectal Cancer Screening Network.
2006 Dutch Society of Gastroenterology.

PEER REVIEWER ACTIVITIES

2009 Gut
BMC Cancer

DANKWOORD

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CURRICULUM VITAE

Lieke Hol werd op 4 maart 1981 geboren te Beilen. In 1999 behaalde zij het gymnasium eindexamen aan het Dr. Nassau College te Assen. Vervolgens studeerde zij geneeskunde aan de Rijksuniversiteit Groningen. Tijdens haar studie nam zij deel aan de International School of Hepatology and Tropical Medicine onder begeleiding van professor C.H. Gips, die het mogelijk maakte haar afstudeeronderzoek te verrichten op de afdeling Hepatologie van het Toronto General Hospital onder begeleiding van professor F. Wong. Ze deed een extra co-schap op de afdeling Cardiologie van het Saint Michael's Hospital te Toronto. Haar oudste co-schap doorliep zij op de afdeling Lever Transplantatie van de Mayo Clinic te Rochester en de afdeling Maag-, Darm- en Leverziekten van het Erasmus MC te Rotterdam, waarna ze cum laude haar artsexamen behaalde. In mei 2006 startte zij met promotieonderzoek naar darmkanker screening onder begeleiding van haar promotoren professor E.J. Kuipers en professor J.D.F. Habbema en haar co-promotor Dr. M.E. van Leerdam. In december 2008 is zij gestart met de opleiding tot Maag-, Darm- en Leverarts vanuit het Erasmus MC (opleider: dr. R.A. de Man) in het Ikazia Ziekenhuis te Rotterdam (opleider: dr. A. Dees).