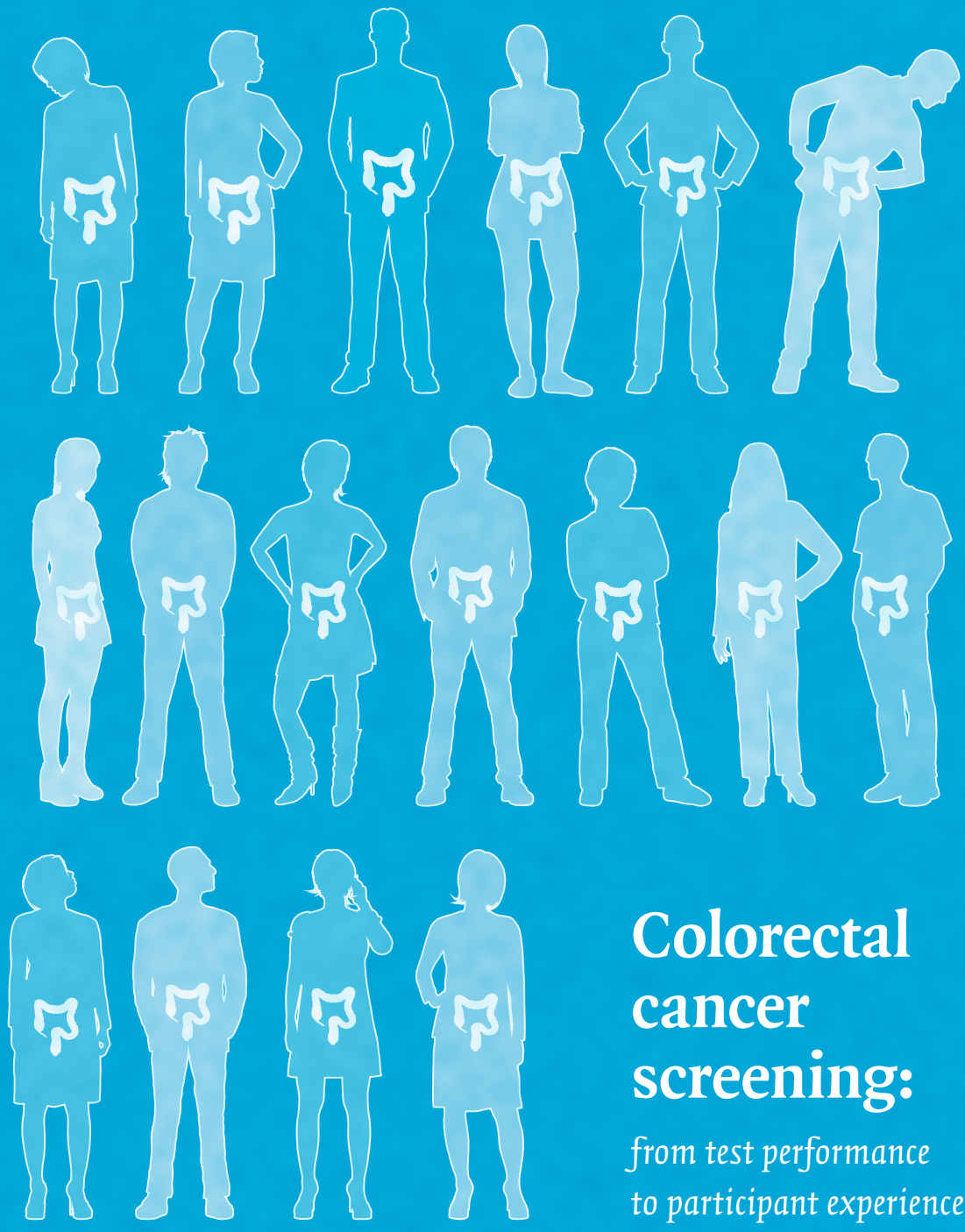

Colorectal cancer screening:

from test performance to participant experience

LEONIE VAN DAM

Colorectal Cancer Screening

From test performance to participant experience

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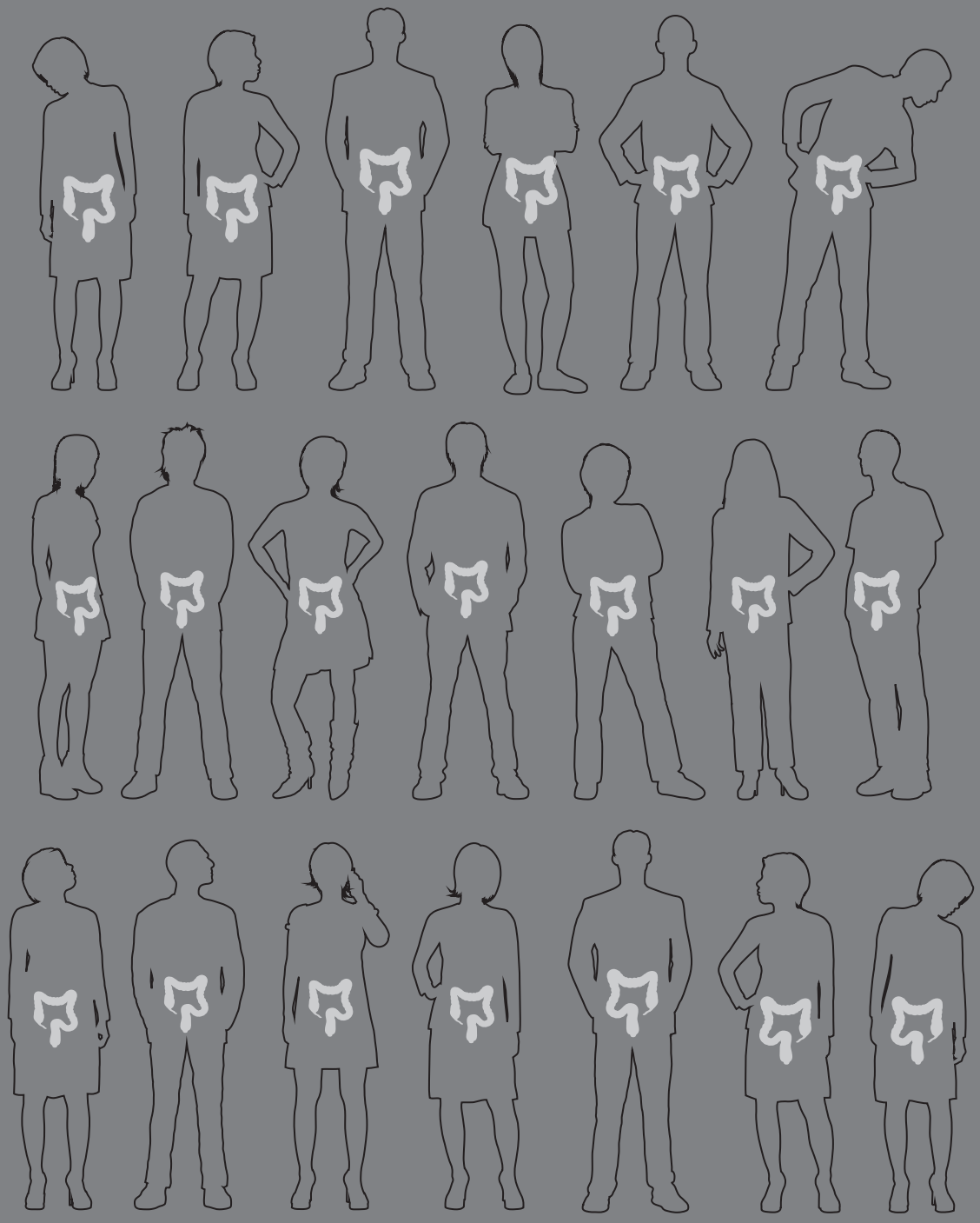

CHAPTER 1

General introduction and outline of the thesis

Adapted from

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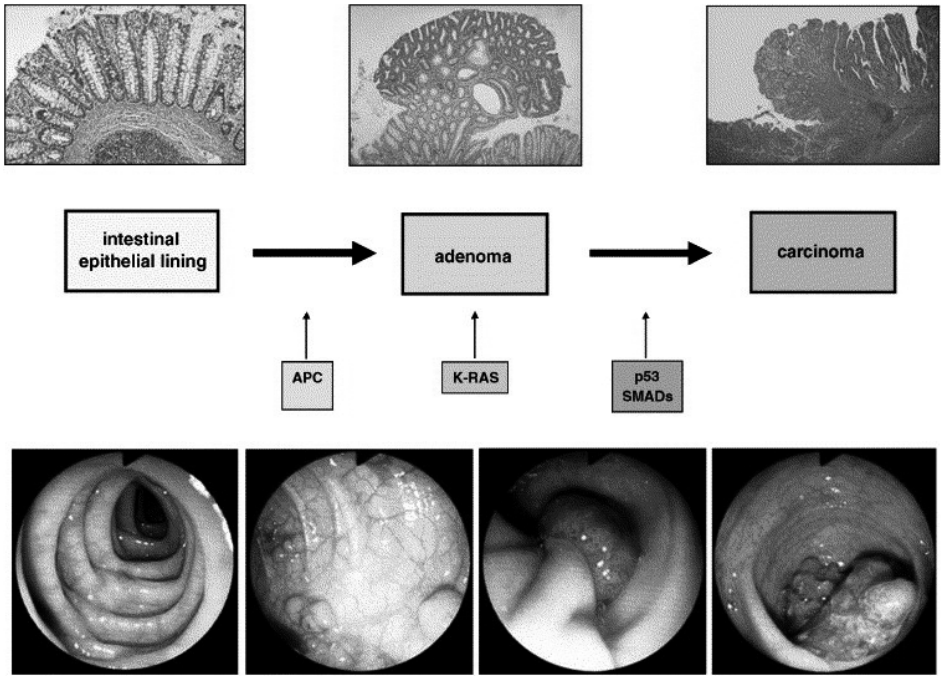
COLORECTAL CANCER

Colorectal carcinoma (CRC) is an important health problem; it is the second most frequently occurring malignancy and the second leading cause of cancer-related death in the Western world.[1] A 2008 study demonstrated that in many European countries CRC mortality rates are decreasing while incidence is rising, leading to an increasing CRC prevalence.[1] Colorectal cancer has a strong correlation with age, with CRC far more frequently occurring in elderly people.[2] Therefore, the ageing of the population will increase the total colorectal cancer burden.[3] Furthermore, CRC is more frequent in males than in females.[2]

CRC originates from mucosal cells in the gastrointestinal tract. The first step in the development of CRC is a hyperproliferation of the epithelium and crypt dysplasia caused by mutations in genes such as the adenomatous polyposis coli (*APC*) gene. This hyperproliferative epithelium can develop into an adenoma (polyp) as a result of genetic mutations in several genes (for instance the oncogene *K-ras*, the tumor suppressor genes *TP53*, *SMAD2*, *SMAD4* and DNA-mismatch repair genes). The genetic mutations result in a decreased apoptosis and an increased cell proliferation and angiogenesis. The acquisition of multiple mutations results in genetic instability as a result of which the adenoma can transform into a carcinoma (adenoma-carcinoma sequence; Figure 1).[4-6]

Figure 1 Adenoma-carcinoma sequence. From Fodde et al. Expression and genomic profiling of colorectal cancer. Biochemica et Biophysica Acta (BBA) - Reviews on Cancer 2007; 1775 (1): 103-107



CRC usually (depending on the DNA mutation involved) develops in a time frame of 10-15 years.[7] This long preclinical stage, starting with the formation and slow progression of a colorectal polyp, offers the opportunity for cancer prevention, by screening and treatment for premalignant lesions and early cancers. The main prognostic factor for CRC is the stage at the time of diagnosis. As CRC symptoms (changed bowel habits, melaena, rectal blood loss, rectal mucus loss, false urge, abdominal fullness, pain, ileus and systemic symptoms like anaemia and weight loss) often occur late in the course of the disease, diagnosis in regular health care is often in a later stage than can be achieved by screening.[8, 9]

American 5-year survival rates (TNM classification) are 93% for stage I, 83% for stage II, 60%% for stage III and 8% for stage IV.[10] Consequently, detection of CRC in an early stage considerably improves prognosis.

POPULATION SCREENING FOR CANCER

Screening for cancer has an extensive history, with screening for cervical cancer being introduced in the United States as early as the 1950s and 1960s[11], and screening for breast cancer in the early 1980s[12]. Colorectal cancer (CRC) screening in the United States experienced a slow start in the early 1990s; but was broadly recommended after evidence from three randomized controlled trials (RCTs) on the effect of faecal occult blood test screening (FOBT) was published in the mid 1990s.[13] The rationale behind all these three cancer screening programs is that early detection (usually before symptoms arise) will prevent morbidity (e.g. less invasive treatment) and mortality.

For a disease to be eligible for screening, several criteria have to be met, that have been summarized by Wilson and Jungner in 1968 and were later updated (Table 1).[14, 15] For colorectal cancer; there is generally consensus that the Wilson and Jungner criteria have been met; resulting in the wide recommendation of colorectal cancer screening.[16-18]

COLORECTAL CANCER SCREENING METHODS

One of the aspects that discern CRC screening from most other types of cancer screening is the availability of multiple screening methods. Screening methods for CRC can generally be divided into two categories; faecal tests (i.e. FOBTs and faecal DNA testing) and structural exams (i.e. sigmoidoscopy, colonoscopy and computed tomography colonography (CTC); Table 1). Those methods differ in many aspects such as invasiveness/burden of the procedure, the certainty the method gives on the presence or absence of CRC (related to the sensitivity and specificity of the method), required screening frequency

Table 1 Wilson and Jungner screening criteria[14,15]

Wilson and Jungner classic screening criteria	Synthesis of emerging screening criteria proposed over the past 40 years
The condition sought should be an important health problem	The screening programme should respond to a recognized need.
There should be an accepted treatment for patients with recognized disease	The objectives of screening should be defined at the outset.
Facilities for diagnosis and treatment should be available	There should be a defined target population.
There should be a recognizable latent or early symptomatic stage	There should be scientific evidence of screening programme effectiveness.
There should be a suitable test for examination	The programme should integrate education, testing, clinical services and programme management.
The test should be acceptable to the population	There should be quality assurance, with mechanisms to minimize potential risks of screening.
The natural history of the condition, including the development from latent to declared disease, should be adequately understood	The programme should ensure informed choice, confidentiality and respect for autonomy.
There should be an agreed policy on whom to treat as patients	The programme should promote equity and access to screening for the entire target population
The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	Programme evaluation should be planned from the outset.
Case-finding should be a continuing process and not a "once and for all" project	The overall benefits of screening should outweigh the harm.

and several other features (e.g. location (at home/hospital/clinic), handling of stool). These aspects of the different screening methods will be discussed below.

Faecal occult blood testing

Stool testing is a widely accepted, non-invasive, home-based technique for colorectal cancer (CRC) screening.[16, 18, 19] FOBT screening primarily aims at early detection of CRC.[19] Traditionally, the guaiac-based FOBT (gFOBT), reacting to the presence of haem, has been used for screening stool samples for the presence of occult blood. More recently, the faecal immunochemical test (FIT), reacting to the presence of globin, has gained an increasing interest due to higher sensitivity and improved detection rate of advanced neoplasia.[20-25] Despite these improvements, sensitivity of FOBTs remains relatively low for CRC and precursor lesions (advanced adenomas).[26] Stool DNA (sDNA) tests have been developed, with a possible superior sensitivity compared to the gFOBT and FIT for detecting CRC as well as advanced adenomas.[27] However, in absence of evidence on the efficacy of sDNA testing in a population screening setting, they are not used on a large-scale yet. Performance of the gFOBT, FIT and sDNA tests depend on program-related as well as test-related factors. Program-related factors include screening interval and

program compliance (the willingness to attend successive screening rounds). All FOBTs have to be followed by colonoscopy in case of a positive test result.

In the Netherlands, the burden of FOBT screening has found to be very low among participants, with a high willingness to attend successive screening rounds; both for gFOBT and FIT screenees.[28]

Both the gFOBT and FIT have to be repeated annually or biennially as single test sensitivity remains relatively low, but program sensitivity (sensitivity when an individual participates in subsequent screening rounds) is higher.[26] The optimal screening frequency of sDNA testing is unknown. In the RCTs carried out for gFOBT and FIT, first round uptake was between 50% and 67%; uptake for subsequent screening rounds depended on the policy for re-invitation.[29] Uptake in population-based screening programmes ranged from 17% to 90% for first round screening; at subsequent screening rounds from 22%–52%.[29] Uptake is usually higher for FIT, which is mainly attributed to the easier and less burdensome stool sampling procedure.[23, 25, 30] For sDNA tests, data on uptake are lacking.

FOBT screening by gFOBT and FIT has been calculated to be at least cost-effective, but probably also cost-saving (i.e. less expensive than offering no screening) due to rising chemotherapy costs.[31, 32] For sDNA screening, data are lacking.

Guaiac-based FOBTs

The most common and traditionally used gFOBTs are the guaiac impregnated Hemoccult II and the more sensitive Hemoccult II SENSA.[26, 33] GFOBTs detect the presence of haem in the faecal sample; however gFOBTs do not specifically detect human haem. When guaiac (present on the test cards) is exposed to hydroperoxidase, haem catalyses its oxygenation which results in a perceptible blue colour change. Performance of gFOBT is limited, as it can also detect haem from upper gastrointestinal bleedings or animal haem (food) in the faeces causing false-positive test results.[34] For most gFOBTs, two stool samples from three consecutive bowel movements are collected at home and sent to a laboratory.

Test performance of the gFOBT depends on several factors related to the tested subject, the method of faecal collection, the test itself and test analysis. With regard to the subject related factors, both dietary factors (e.g. consumption of red meat because of haem presence, several fresh fruits and vegetables given peroxidase activity) and medication (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs)) have been suggested to increase the risk of false-positive test results. Vitamin C may cause false-negative results given its capacity to block the hydroperoxidase reaction.[35] Potential interference of plant peroxidases can be avoided since they break down with time, so if the faeces on the gFOBT are dried for at least 48 hours before test analysis, dietary restrictions with regard to peroxidase-rich fruits and vegetables are unnecessary.[36] A meta-analysis concluded that modest dietary restrictions do not influence uptake of the test and that there is little evidence for dietary restriction to influence positivity rates of Hemoccult

or Hemoccult II.[37] However, strict dietary and medication restrictions may influence test uptake. The evidence on the effect of vitamin C use on test performance was inconclusive.[37] The use of aspirin or NSAIDs does not seem to increase false-positivity of the Hemoccult II and Hemoccult II SENSA.[38, 39] Thus, physicians do not need to advise participants to restrict their diet and/or medication prior to gFOBT, although usually advised otherwise by test manufacturers. Performance of both the gFOBT and FIT test can also be influenced by the composition of faecal samples and the sample volume.[29]

Furthermore, there are test-related factors influencing test performance. An important determinant of test performance is whether rehydration (adding water to the stool specimen before processing) is applied or not. Rehydration of Hemoccult II has been shown to improve test sensitivity for CRC[40, 41], but reduce specificity[41]. In line with these results, another study found rehydration to increase the positivity rate, but decrease the positive predictive value (PPV).[42] As rehydration also decreases test readability, it is nowadays no longer recommended.[35, 43, 44] The level of moisture also influences performance, with a decrease in positive rate with increasing moisture content.[45] Furthermore, the threshold chosen (cut-off; e.g. the number of slides that have to be positive in order to refer an individual for colonoscopy) for a positive test is an important determinant of test performance.[40, 41, 46-51] Performance of gFOBT also depends on the accuracy of test result interpretation, which is observer-dependent but may be improved by training.[52, 53]

Sensitivity and specificity of the gFOBT highly varies between studies. In a 2008 review, sensitivity ranged from 13–37% for non-rehydrated, 50–86% for rehydrated Hemoccult II and 72–79% for Hemoccult II SENSA.[54] GFOBT has been shown to reduce CRC mortality by on average 16%.[41, 46, 47, 55]

Faecal immunochemical tests

FITs have several advantages over gFOBT among which the higher sensitivity and easier stool collection method.[20-25, 56] FIT usually aims at the detection of human globin by means of specific antibodies using enzyme-linked immunosorbent assay (ELISA)[57], although they may also aim at for example the detection of the haemo-/haptoglobin complex[58, 59]. Globin present in blood from the proximal gastrointestinal tract is gradually digested during its passage through the intestine, making FIT rather specific for bleeding from the distal gastrointestinal tract.[29] FIT allows for the detection of blood at lower concentrations than gFOBT.[29] Furthermore, no dietary restrictions are required given the fact that the FIT specifically detects human haemoglobin and no peroxidase activity is involved, thereby improving specificity. Medication restrictions also seem to be unnecessary. One study suggested that NSAID or aspirin use increased the sensitivity of FIT without a decrease in specificity[60], but the study was limited by the low number of NSAID users[57]. Performance of the FIT is mainly determined by factors related to sample collection, the test itself and factors related to test analysis.

Both quantitative and qualitative FITs have been developed. Qualitative tests require a visual interpretation of test results as positive or negative.[61] Quantitative FITs are analysed automatically, providing a value for the amount of haemoglobin found in the stool sample.

Qualitative FITs allow for simple, office-based analysis. There are large differences in diagnostic performance between different test variants of the qualitative FIT[24, 62], which seems mainly to reflect the differences in cut-off level as pre-defined by the manufacturer[61]. As for gFOBT, interobserver variations in interpretation of the qualitative FIT results may influence performance.

Quantitative FITs have important advantages over qualitative FITs by using automated analysis, thereby removing interobserver variation in interpretation of test results, improving reproducibility and allowing for high-throughput testing.[58] There are currently many FIT kits marketed, with different antigen target stability and sampling methods. An important advantage of the quantitative FIT is that the quantitative nature allows for selection of the optimal cut-off level above which the FIT is considered positive and individuals are referred for colonoscopy; this level can be adjusted given colonoscopy capacity and/or background incidence in a certain population.

Performance of the FIT also depends on the number of samples. A lot of research is carried out into the optimal number of stool samples.[63-69] Three cost-effectiveness analyses found a favourable cost-effectiveness of the two day FIT to both the one and three day FIT[48, 70, 71], another study found that it is more cost-effective to increase the number of screening rounds rather than the number of samples per round[72].

A review including studies up to 2006, including nine fair or good quality studies on FIT performance, found that sensitivity and specificity varied between FITs, with sensitivity ranging between 61%–91% for CRC and 27–67% for large adenomas, and specificity ranging between 91–98%.[73]

Stool DNA tests

SDNA tests detect specific mutations (known alterations in the adenoma-carcinoma sequence), in cellular DNA excreted in stool, that are associated with CRC development. Adenoma and carcinoma cells with DNA mutations are continuously shed into the large bowel and passed into the faeces.[35] Human DNA can be differentiated from faecal bacterial DNA since human DNA is stable in stool.[35]

SDNA tests are generally subdivided into first and second generation tests, with important differences in the utilised panel of markers.[26, 27, 57] A sDNA test usually aims at the detection of multiple gene mutations, since there is not one single mutation present in all advanced adenoma or CRC cells.[35]

Many first generation tests used the multimarker panel PreGen-Plus.[74-78] This test consists of a multimarker panel that aims at the detection of 21 point mutations in the *K-ras*, *APC*, *P53* genes; a probe for *BAT-26* (marker for microsatellite instability); and a marker

of DNA integrity analysis.[35] In the past five years, research has focused on improving marker panels by identifying new markers. In this respect, the gene hypermethylation pathway has gained major interest, since it seems a much more common pathway than previously assumed.[57] Several markers aiming at hypermethylated genes have been developed. The currently used panels of DNA markers seem to detect the majority, but not all CRC.[35] Stool sample processing and preservation are other determinants of sDNA test performance and therefore targets for improvement[35], although important improvements have already been realized.[79, 80] Although this seems promising, there are several reasons for the currently limited application of sDNA tests. First of all, optimisation of new marker panels and assay platforms is advised prior to widespread implementation of next-generation stool DNA testing.[27] Secondly, high throughput systems are required for analysing large numbers of samples with high precision.[27] There are uncertainties about the cost-effectiveness of sDNA tests, which should be assessed critically before implementation.[27] The ideal number of stool samples and screening interval are other issues to be addressed.[26] Thirdly, these tests need to be assessed in a population screening setting to understand performance characteristics. A last issue is the implication of positive sDNA test results without identifiable colonic abnormality.[35] SDNA tests may possibly also detect supracolonic cancers (e.g. oropharynx, esophagus, stomach, pancreas, gallbladder) given the fact that these cells may survive into the faeces.[27, 81] Population-based studies are required to accurately establish sDNA test performance in average risk-subjects, and they are currently underway.[79]

Of the two studies performed among average-risk subjects, aged 50-80 in one study and above 50 years of age in the other, one study found the positivity of the sDNA in average-risk subjects to be 18%, accompanied by a sensitivity of 52% for CRC and 15% for advanced adenomas.[77] Specificity was 94%. The second study found a sensitivity for CRC of 20%, with a 96% specificity.[74] In other, usually small-scale, studies with often mainly symptomatic subjects, sensitivity for CRC ranged between 62–97% for first-generation sDNA tests, accompanied by specificities of 93–100%.[57] Sensitivity of second generation sDNA tests in small scale studies with symptomatic subjects generally ranges from 42–96%, with specificities usually between 77–100%.[57]

Flexible sigmoidoscopy

Flexible sigmoidoscopy (FS) is an invasive, hospital-based endoscopic procedure, examining the last 60 centimeter (up to the splenic flexure) of the colon. FS usually takes about 15 minutes. The preparation is most often an enema, administered at home, and fasting a few hours prior to the procedure. FS is usually performed without sedation. During the examination, CRC precursor lesions (polyps) can be directly removed, thereby CRC can possibly be prevented. Those with a positive FS (although under debate, usually defined as advanced neoplasia (most commonly defined as an adenoma ≥ 10 mm, an adenoma

with ≥ 25% villous histology, or high-grade dysplasia), or three or more adenomas, and those with CRC given the higher risk of synchronous proximal advanced neoplasia[82-84]) are referred for colonoscopy. An Australian study found that readiness to attend a successive screening round was high for sigmoidoscopy screening.[85] A Dutch study found that 13% of FS screenees reported the examination to be burdensome.[28] Eighty-four percent of FS screenees said to be willing to attend a successive screening round. FS needs to be repeated every five to ten years.

One-time sensitivity of FS is estimated to be >95% for CRC in the distal colon and 30-70% for advanced adenoma.[86]

In the recent years, several trials on the effect of FS screening have been published. The first trial published was a Norwegian RCT of once-only FS screening in men and women aged 55-64.[87] The median follow-up was seven years for cumulative CRC incidence. This study found no difference in cumulative incidence between the screening and control group (134.5 and 131.9 cases per 100,000 person years respectively). They found a trend towards reduced CRC mortality in intention to screen analysis, with a hazard ratio (HR) of 0.73 (95% confidence interval (95%CI) 0.47-1.13). In per protocol analysis, the CRC mortality was significantly reduced among attendees (HR 0.41, 95%CI 0.21-0.82).

The second trial published concerned a RCT of once-only FS carried out in the United Kingdom inviting men and women aged 55-64, with a median follow-up of 11.2 years.[88] They found in intention-to-treat analyses that after a single FS, CRC incidence was reduced by 23% (HR 0.77; 95%CI 0.70-0.84) and mortality by 31% (HR 0.69; 95%CI 0.59-0.82). In per protocol analyses, incidence among those screened was reduced by 33% (HR 0.67; 95%CI 0.60-0.76) and mortality by 43% (HR 0.57; 95%CI 0.45-0.72).

A third Italian RCT on once-only FS, also conducted among men and women aged 55-64, had a mean follow-up of 10.5 years for incidence and 11.4 for mortality.[89] They found in intention-to-treat analyses a 18% (rate ratio (RR) 0.82; 95%CI 0.69-0.96) mortality reduction in the intervention group, while the mortality rate was not significantly reduced. In per-protocol analysis, both incidence and mortality were significantly reduced among those screened (31%, RR 0.69; 95%CI 0.56-0.86 versus 38%, RR 0.62; 95%CI 0.40-0.96, respectively).

The last RCT, carried out in the US, randomized men and women aged 55-74 years into repeat screening at three or five years, or usual care.[90] The median follow-up was 11.9 years. In the intervention group, they found a 21% (relative risk 0.79 95%CI 0.72-0.85) CRC incidence reduction and a 26% (relative risk 0.74; 95%CI 0.63-0.87) CRC mortality reduction.

In FS screening, the most frequent complications are perforation and bleeding. Perforation occurs in approximately 1 in 25.000-50.000 procedures, the rate of bleeding after polyp removal is <1%.[91]

Uptake of FS screening is around 32-84% in RCTs (with high screening rates coming from studies that invited only volunteers or those that gave a positive response to

a questionnaire determining interest in participation)[23, 29, 92-97], and between 7-55% in population based programmes[29, 98-101].

Screening by flexible sigmoidoscopy is estimated to be at least cost-effective, but probably also cost-saving taking into account rising chemotherapy costs due to newer, more effective treatments.[31, 32, 102]

Colonoscopy

Colonoscopy is a hospital-based examination that is both used for screening purposes and as the gold standard for CRC diagnosis; so therefore it is the examination of choice for those with positive findings during FOBT, FS or CTC screening.

During colonoscopy, the entire colon is examined (up to the cecum/terminal ileum). Prior to the procedure, a purgative bowel preparation is required, including fasting and drinking of usually 2-4 litres laxative fluids. This bowel preparation is often considered to be the most burdensome aspect of the entire screening procedure.[103-105] Colonoscopy is often performed under conscious sedation (e.g. intravenous midazolam and fentanyl). CRC precursor lesions (polyps) can be directly removed during colonoscopy, so important advantages are that no additional investigation is required and that it is possible to obtain histology diagnosis. By directly removing precursor lesions, there is also a preventive effect for the development of CRC. A Dutch study found that invitees to colonoscopy screening expected the procedure to be more burdensome than what they experienced.[103] The majority of participants (96%) would probably or definitely take part in a next screening round. A randomized Australian study compared screenee acceptability of FOBT, flexible sigmoidoscopy, colonoscopy, CTC, or a choice of methods.[85] Pain ratings were highest for CTC, somewhat lower for flexible sigmoidoscopy, and lowest for colonoscopy. This may be due to the fact that colonoscopy is usually performed under conscious sedation. Readiness to attend a successive screening round was high for all methods.

If no abnormalities are found during colonoscopy, evidence indicates that the examination only needs to be repeated after ten years.[35, 106] A German study even suggests that the risk of developing CRC after a negative colonoscopy is so low, that a once-only colonoscopy may suffice.[107]

Sensitivity is assessed to be 95% for CRC and 88-98% for advanced neoplasia[86], depending on the skills of the endoscopist. No data from RCTs on the mortality reduction of colonoscopy screening are available yet. Based on modelling, colonoscopy screening is expected to reduce CRC incidence by 76-90%[108] and CRC mortality by 65-84%[109]. Results of the randomised NordICC-trial and a Spanish trial[110] are expected to provide data on the effectiveness of colonoscopy screening in reducing colorectal cancer-related mortality. The mortality reduction seems be highest for left-sided CRC.[111, 112]

Possible complications of colonoscopy are bleeding, perforation, and, although uncommon, death. The perforation rate is 1 in 1400 for overall colonoscopies and 1 in

1000 for therapeutic colonoscopies.[113] Mortality is 0% in most studies, with the highest reported being 0.02%.[113]

Participation in colonoscopy screening in population-based studies ranges from 18–40%, in Germany annual participation is 2–3%, with a cumulative 6-year participation of 16-17%.[85, 94, 114-117] Colonoscopy is estimated to be at least cost-effective, while the literature is currently inconclusive on whether colonscopy screening is cost-saving.[32, 102, 118]

Computed tomography colonography

CTC is also a hospital based examination, using X-ray beams for the production of tomographic images, enabling 2- and 3-dimensional visualization. The entire colon and rectum are visualized.

Prior to the procedure, bowel preparation is required. Both purgative (equal to colonoscopy) and limited (fecal tagging) bowel preparation are available. Limited bowel preparation is a relatively new, promising alternative for the currently used cathartic bowel preparations, although not currently recommended as there is no evidence from directly comparative studies yet regarding diagnostic accuracy.[115, 119] Fecal tagging consists of drinking small amounts (e.g. 50 mL) of iodinated contrast on the day prior to CTC, and some more on the day of the examination. A low fibre diet is required prior to procedure.

The procedure is usually performed without sedation. Carbon dioxode is insufflated into the bowel through a small tube, in order to achieve adequate colonic distension, after intravenous administration of a spasmolytic agent (i.e. butylscopolamine or (when contraindicated) glucagonhydrochloride.

In case of colonic abnormalities on CTC, a colonoscopy is performed.

A large study with individuals undergoing same day CTC and colonoscopy assessed sensitivity and specificity for large adenomas (≥10 mm) to be 94% and 96% respectively, and for adenomas ≥6mm 89% and 80% respectively.[120]

There is general agreement that polyps with a size of more than 10mm should be referred for colonoscopy.[119] The latest guidelines from the American Gastroenterology Association advise to report all polyps equal to or lager than 6mm. There is still debate on the significance of laesions up to 5mm.

There are no RCT data on mortality reduction with CTC screening available yet. Based on modeling, CTC is effective in reducing CRC incidence (estimated to be 40-77%) and CRC mortality (58-83%).[121]

Perforation risk in screening individuals is around 0.005%.[122, 123] Exact cancer risk due to radiation exposure is unknown.[124] A single CTC was estimated to increase the life-time cancer risk of a 50-year old by 0.13-0.15% and a 70-year old by 0.07%, although currently lower radiation doses are used.[124, 125]

CT-colonography also allows for the detection of intra-abdominal, extracolonic abnormalities. A recent review concluded that in CRC screening populations, 4.5-11% of screenees had (potentially) important extra-colonic findings precipitating additional testing.[126] More research on the impact of extra-colonic findings is warranted.

Participation usually ranges from 16-28% in population-based screening studies.[85, 115, 127, 128] CTC screening has been shown to be cost-effective in studies published so far.[121, 129]

SUCCESSFUL SCREENING

The success of a screening program is often expressed in participation rates. Participation is an important marker; since an aim of population screening is to lower the burden of disease for the entire target population and therefore a screening programme with a low participation rate can be considered unsuccessful.

Uptake is influenced by test-related factors (e.g. burden of the test, type of test (for FOBTs)), organizational factors (e.g. preannouncements/reminders, method of invitation, ability to perform the test at home), and subject-related factors (e.g. demographics, barriers (e.g. time-requirements), psychosocial factors including knowledge and awareness of CRC and CRC screening, attitudes towards it, and perceived susceptibility).

Although increasing uptake for CRC screening is an important target, people make an autonomous decision on participation after weighting the pros and cons of screening.[130] The consistency between an invitees' attitude and subsequent screening behavior is therefore an important marker for success of CRC screening programmes.[131] It is important to reveal the reasons for participation and non-participation. Reasons that may be modifiable (e.g. organizational factors, perceived barriers, lack of knowledge) require action, while others should be respected (well-informed decision on (non-) participation).

CONCLUSIONS

Colorectal cancer is a disease with high incidence and mortality. Screening can significantly reduce CRC mortality, and can be cost-saving. Several screening methods are suitable for CRC screening, with considerable differences regarding their nature (including the burden and accompanied risks), the diagnostic value, and potential effect on reducing CRC-related mortality. Therefore, gaining insight in aspects determining population preferences for and participation in screening with the different methods is of importance for the future of CRC screening.

AIMS OF THE THESIS

The aim of this thesis is to explore various aspects of CRC screening that contribute to decision making on CRC screening for policy makers and individuals deciding on CRC screening participation. These include diagnostic accuracy, screening test preferences, reasons for (non)-participation and time-requirements of different CRC screening strategies (FOBT, FS, colonoscopy and CTC). We hereto collected and analyzed data from the pilot CRC screening programmes conducted in the Rijnmond, and partly, Amsterdam region in the Netherlands. Furthermore, given the important differences between screening strategies, we aim to clarify ethical aspects on the optimal screening policy, specifically on the issue of offering a single screening test to the target population or a choice between strategies.

OUTLINE OF THE THESIS

Several screening tests are eligible for colorectal cancer screening, including FOBT, FS, colonoscopy and CTC. Worldwide, there is much variation in the screening method chosen for population based-screening. In the Netherlands, pilot studies on the optimal screening strategy have been conducted, comparing FOBT and FS screening, and colonoscopy and CTC screening. As these examinations differ considerably, this thesis aimed to investigate different aspects that determine either policy makers' or population preferences for certain screening tests.

When this thesis is printed, the roll-out of a nation-wide call-recall screening programme in the Netherlands is about to start. The Minister of Health, Welfare and Sports advised in 2011 to implement a CRC screening programme with biennial FIT screening, for all adults aged 55-74.[132] The Health Council advised that biennial FIT screening is, at the moment, the best strategy given the test performance and acceptance of the test.[132] In Chapter 2, the results of a systematic review on the positivity rate, detection rate, and positive predictive value of the different FIT brands for advanced neoplasia are presented. Of the far majority of population-based FIT screening studies, only these outcome parameters are available as colonoscopy-controlled trials are scarce.

As previously shown, one of the important Wilson and Jungner screening criteria concerns the acceptability of a test to the population.[15] They mention that "the acceptability of a test is related to the nature of the risk and to the way in which the ground is prepared previously by health education". Three chapters of this thesis focus on aspects related to the acceptability of a test. The willingness to undergo screening is influenced by perceived benefits and drawbacks of participation, and thereby also by knowledge and awareness of CRC and all related aspects.

In Chapter 3 the results of a study on aspects that influence population preferences for colorectal cancer screening by FOBT, FS and colonoscopy are presented. Gaining insight into factors that influence screening preferences and thereby most likely screening participation is essential in order to make a choice between screening options. We investigated these preferences using a discrete choice experiment (DCE); a method that has its origin in economic research but is increasingly used for health care purposes.

In order to understand the determinants of the acceptability of screening tests, it is further important to survey actual experiences with the screening tests among those participating, and reasons not to participate among non-participants. This allows for determining barriers for participation and thereby targets for improvement of screening programmes. In Chapter 4, the results of a questionnaire study on reasons for and determinants of participation and non-participation in FOBT and FS screening are presented.

Both colonoscopy and CTC screening are promising and used on a large scale in the United States. For both screening methods, time-requirements may be an important barrier for participation as they are both potentially time-consuming (preparation, travelling to the hospital, recovery). The time required for participation is important both from the participant view and from a collective view; namely economic expenses due to a loss of productivity. For colonoscopy and CTC screening, we studied time requirements and health effects of participation (Chapter 5).

The unique feature of the availability of multiple screening strategies for colorectal cancer in contrast to cervical and breast cancer screening requires deliberation on whether individuals should be given a choice between them. From the foregoing, it is obvious that there are important differences between the screening strategies, and it is imaginable that preferences regarding these strategies may be personal. In the last chapter (Chapter 6), the question whether individuals should be offered a single screening strategy or given a choice between available screening methods based on the currently available evidence is discussed from an ethical point of view.

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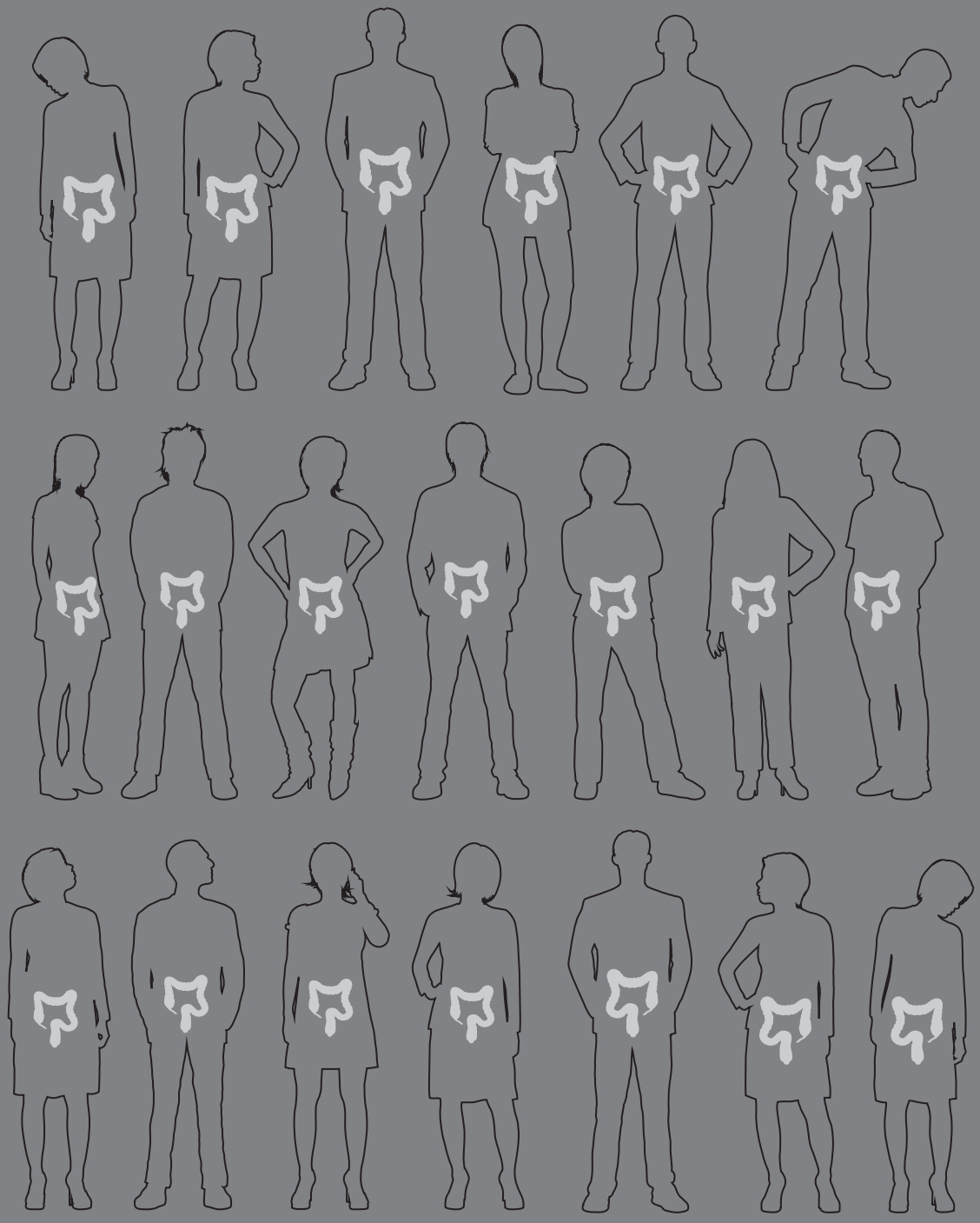

CHAPTER 2

Fecal immunochemical tests for colorectal cancer screening in average-risk individuals: A diagnostic test accuracy review

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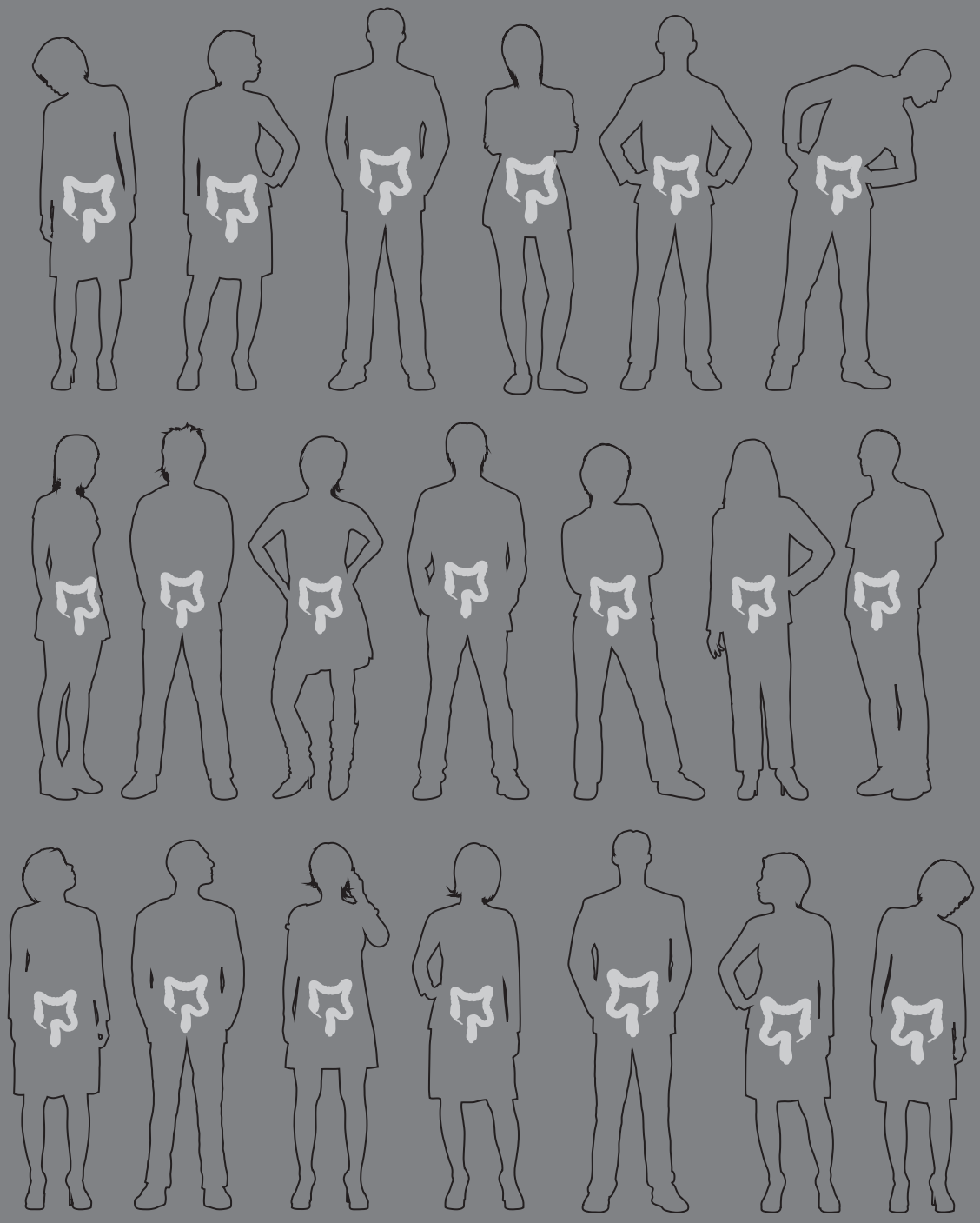
Submitted



CHAPTER 3

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

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ABSTRACT

Introduction: In many countries uptake of colorectal cancer (CRC) screening remains low.

Aim: 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.

Methods: A discrete choice experiment was conducted among subjects in the age-group of 50 – 75 years, including both screening-naïve subjects and 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.

Results: 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.

Conclusion: This study shows that especially type of bowel preparation, risk reduction of CRC-related death 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 (EU), 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).[5,11,12] There are several methods available for CRC screening. The various types of faecal occult blood tests (FOBTs) primarily aiming at the early detection of CRC, whereas endoscopic 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[18;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.[21] 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 338.000 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 guaiac-based FOBT (gFOBT), faecal immunochemical test (FIT) or FS.[13]

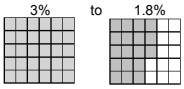
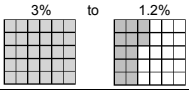
Invitation of subjects

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

Figure 1 Choice set example.

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)*

duration).[26] 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.[26] 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.

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. $2^{3}*4^{4}$) pos-

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)	

sible 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.[27] 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;[28]) 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 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[29]) and a question assessing experienced difficulty of the question-

naire (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 MC (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[30;31], 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.[32;33]

$$P_{participation} = \frac{1}{(1+e^{\wedge -v})}$$

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, the location hospital, preparation by an enema and a duration of 30 minutes. For colonoscopy we used mild pain, a small risk of complications, the 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 and 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) than screening-naïve individuals (31%; 156/500) (Figure 2, 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

Figure 2 Overview of subjects accessing the study

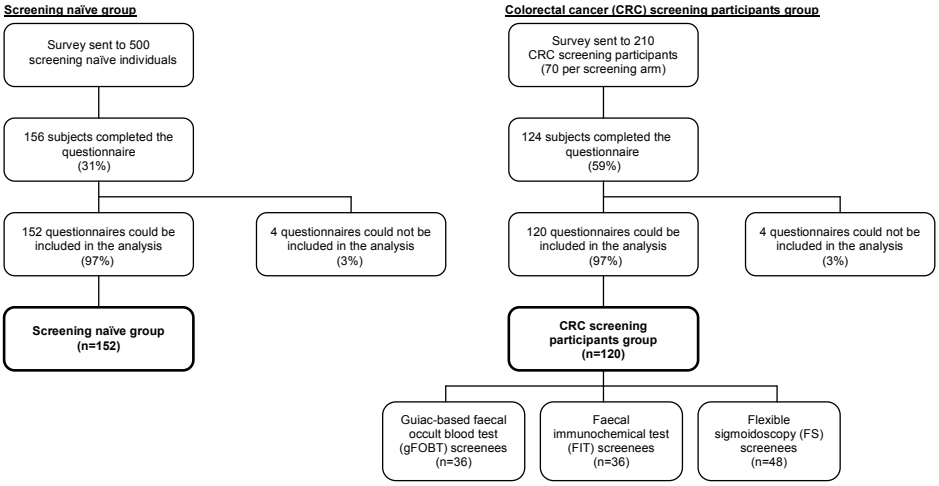


Table 2 Respondent characteristics

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) (n - %)			p=0.84
Yes	19 (12.5)	18 (15.0)	
No	115 (75.7)	88 (73.3)	
Unknown	18 (11.8)	14 (11.6)	
Generic health status (EQ-5D) summary score (mean - SD)	0.92 (0.11)	0.93 (0.12)	p=0.48

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).

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

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 litre of fluid. 12 hours fasting	-0.51	(-0.72 to -0.29)*	-0.22	(-0.45 to 0.01)
Drinking of 4 litres 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

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 litre 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 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 litre of fluid' instead of a preparation with

'4 litres of fluid' (*p*-values <0.001). Preparation with an 'enema' and '0.75 litre of fluid' was 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.

Table 4 Individuals' trade-offs between risk reduction and different aspects of a colorectal cancer (CRC) screening programme.

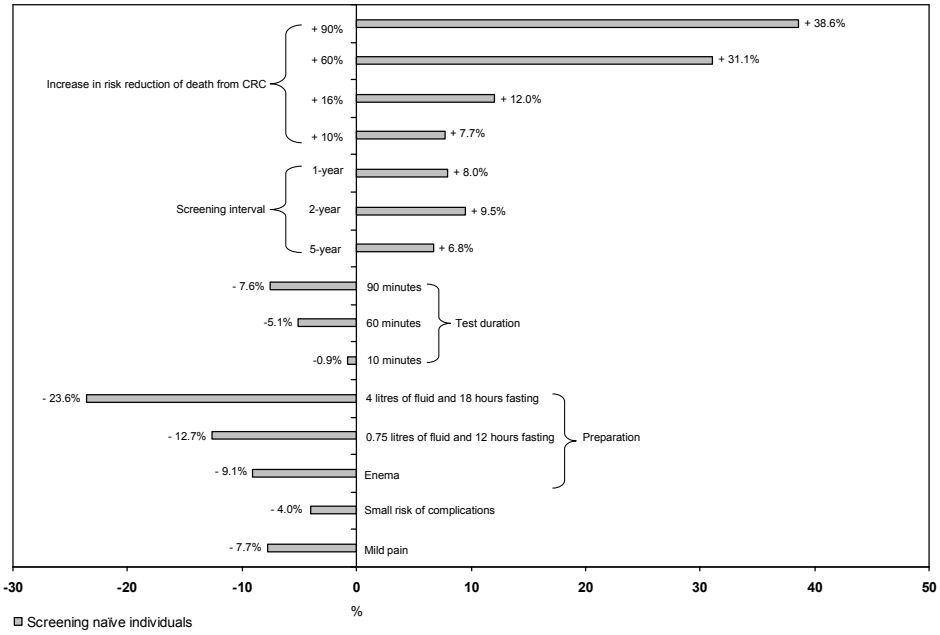
Levels	Screening naïve	Participants	Interpretation note
	% of additional relative risk reduction respondents think a test should generate....		
Pain			.. in order to undergo a test that causes mild pain instead of a test that causes no pain
None (ref)			
Mild pain	10% (6-13%)	9% (4-13%)	
Risk of complications			.. 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 litre of fluid and 12 hours fasting	16% (9-23%)	8% (0-17%)	
Drinking of 4 litres 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

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 5-yearly FS screening and 71% for 10-yearly colonoscopy screening (risk reduction of CRC-related death respectively 16%[34], 59%[5] and 74.5%[35]). The effects of changing the CRC screening programme characteristics on average expected uptake of CRC screening are shown in Figure 3.

Figure 3 Effects of changing the screening programme characteristics on the average probability of participation in colorectal cancer (CRC) screening (56.2%), as predicted by the multinomial logit model.



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 atten-

dance 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.[36-41] Our finding that individuals attach much importance to CRC mortality reduction by a screening method is consistent with the results of previous studies.[36;41;42] 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.[43] One study among Danish individuals and another among both American and Canadian individuals could not confirm preferences for shorter CRC screening intervals.[36;40] 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.[44;45] 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.[46] 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.[18;47;48] 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[49].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.[50]

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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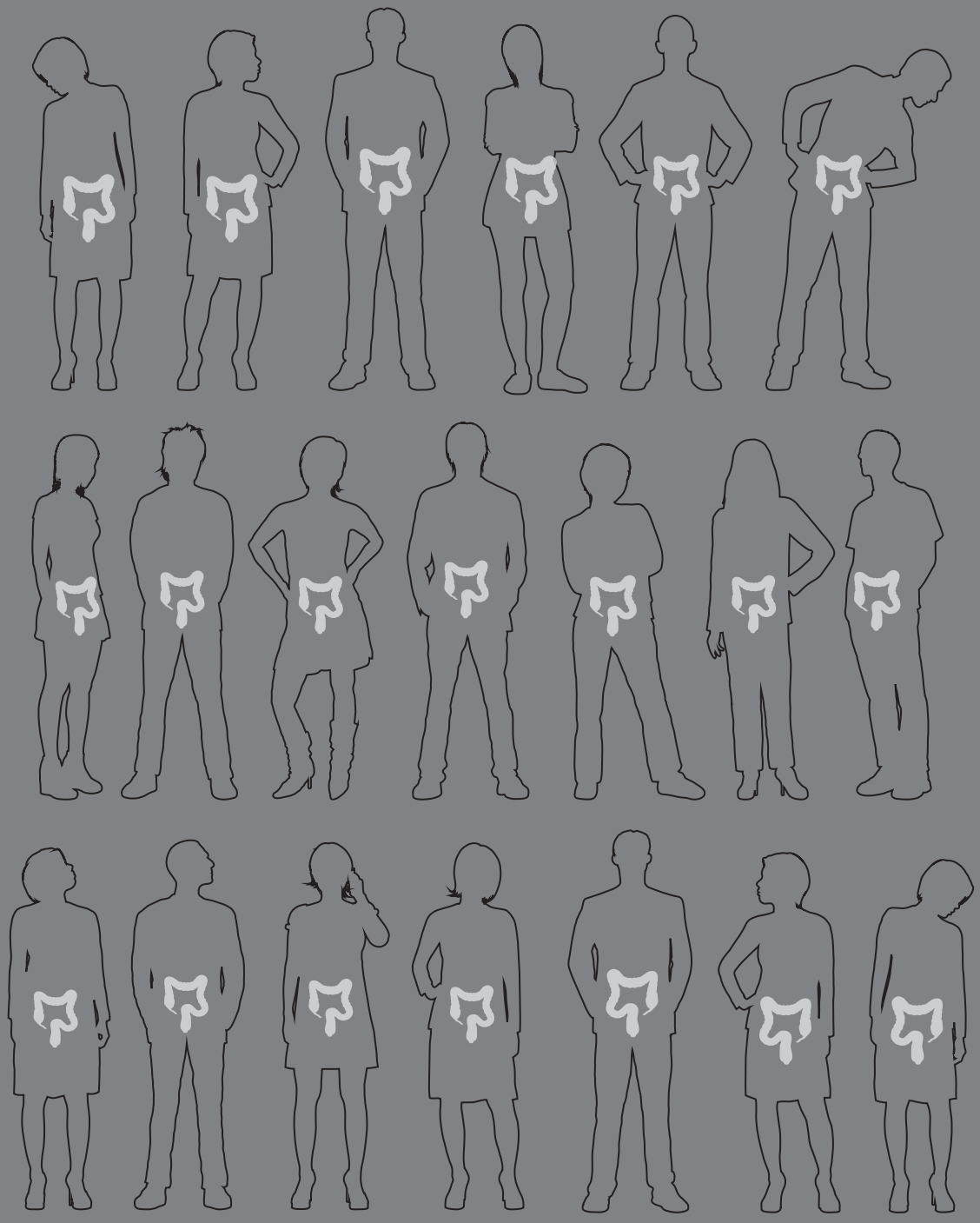

CHAPTER 4

What influences the decision to participate in colorectal cancer screening with faecal occult blood testing and sigmoidoscopy?

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ABSTRACT

Introduction: Uptake is an important determinant of the effectiveness of population-based screening. Uptake of colorectal cancer (CRC) screening generally remains suboptimal.

Aim: To determine factors influencing the decision whether to participate or not among individuals invited for faecal occult blood test (FOBT) or flexible sigmoidoscopy (FS) screening.

Methods: A questionnaire was sent to a stratified random sample of individuals aged 50–74, previously invited for a randomised CRC screening trial offering FOBT or FS, and a reference group from the same population not previously invited (screening-naïve group). The questionnaire assessed reasons for (non)-participation, individuals' characteristics associated with participation, knowledge, attitudes and level of informed choice.

Results: The response rate was 75% (n = 341/452) for CRC screening participants, 21% (n = 676/3212) for non-participants and 38% (n = 192/500) for screening-naïve individuals. The main reasons for FOBT and FS participation were acquiring certainty about CRC presence and possible early CRC detection. Anticipated regret and positive attitudes towards CRC screening were strong predictors of actual participation and intention to participate in a next round. The main reason for non-participation in FOBT screening was lack of abdominal complaints. Non-participation in FS screening was additionally influenced by worries about burden. Eighty-one percent of participants and 12% of non-participants made an informed choice on participation.

Conclusion: Only 12% of non-participants made an informed choice not to participate. These results imply that governments and/or organizations offering screening should focus on adequately informing and educating target populations about the harms and benefits of CRC screening. This may impact uptake of CRC screening.

INTRODUCTION

Colorectal cancer (CRC) is an important health problem in the Western world.[1] CRC screening is effective in reducing CRC-related mortality,[2–6] and therefore widely recommended.[7–10] CRC screening through various types of faecal occult blood tests (FOBTs) primarily aims at the early detection of CRC, whereas endoscopic examinations (flexible sigmoidoscopy (FS), colonoscopy) are effective for both early detection of CRC and removal of premalignant lesions.

Uptake is an important determinant of the effectiveness of population screening programmes on a population level. In many countries, the consistent uptake of CRC screening, both of primary as well as repeat screening, has remained suboptimal.[11] Furthermore, uptake of endoscopic screening is generally inferior to FOBT screening.[12–14] Hence, increasing uptake of CRC screening is vital for reducing CRC related mortality.[15] Uptake is influenced by test-related factors (e.g. burden of the test, type of test (for FOBTs)), organizational factors (e.g. preannouncements/reminders, method of invitation and ability to perform the test at home), and subject-related factors (e.g. demographics, barriers (e.g. time requirements), psychosocial factors including knowledge and awareness of CRC and CRC screening, attitudes towards it and perceived susceptibility).

While increasing CRC screening uptake is an important target, people make an autonomous decision on participation after weighting the pros and cons of screening.[16] The consistency between an invitees' attitudes and subsequent screening behaviour is an important marker for success of CRC screening programmes.[17] It is therefore imperative to reveal the reasons for participation and non-participation. Especially reasons that may be modifiable (e.g. organizational factors, perceived barriers and lack of knowledge) and require action, while others should be respected (well-informed decision on (non-) participation).

The aim of our study is to determine factors influencing participation and non-participation among individuals invited for CRC screening within a randomised trial comparing FOBT and FS screening. A reference group of screen naïve individuals was included. Furthermore, we evaluated whether the decision (not) to participate was well informed.

MATERIALS AND METHODS

Study population

Between March 2009 and December 2010, a questionnaire was sent to individuals previously invited for a randomised CRC screening trial and to a reference group of individuals not previously invited for CRC screening. Within this CRC screening trial, average risk

individuals aged 50–74 years, randomly selected from population registries, had been randomised 1:1:1 and invited to participate in guaiac-based FOBT (gFOBT), faecal immunochemical test (FIT) or FS screening.[13] All FIT invitees were invited for a next (second) screening round.[18] Importantly, individuals who declined FS screening subsequently received an invitation for FIT screening.[19] The study protocols are described in detail elsewhere.[13,18,19] The socio-economic status (SES) was based on the data of Statistics Netherlands (www.cbs.nl), providing average SES per postal code area, each representing small neighbourhoods.

From the participants and non-participants in all screening arms of the trial, a random sample stratified for sex and SES was drawn to ensure sufficient data from both genders and all socio-economic classes. The questionnaire was sent to (1) participants of FOBT screening ('FOBT participants'); (2) non-participants of FOBT screening ('FOBT non-participants'); (3) participants of FS screening ('FS participants'); (4) non-participants of FS screening who did attend subsequent FIT screening ('Declined FS, accepted FOBT') and (5) non-participants of FS screening who also declined the subsequent FIT screening invitation ('Declined both FS and FOBT'); (Fig. 1). The reference group consisted of 500 screening naïve individuals ('Screening naive'), randomly selected from the same target-population, and also stratified for sex and SES.

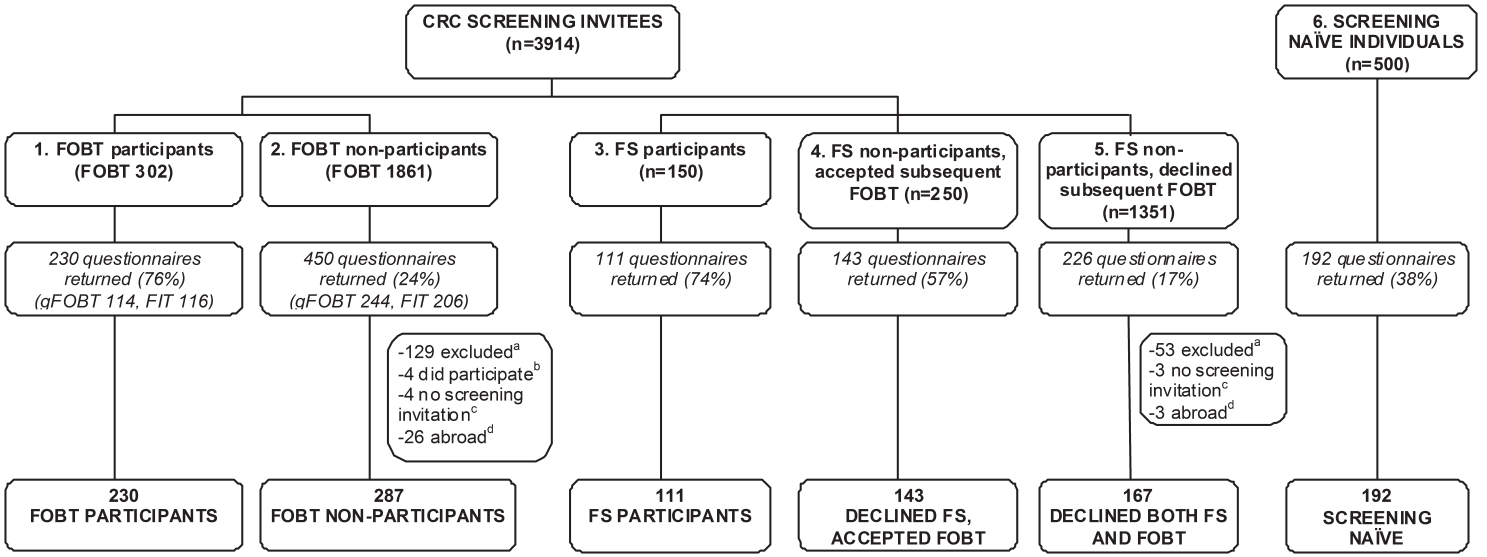
Invitation of subjects

Subjects received a preannouncement by mail, including a reply card that could be returned if individuals did not want to receive the questionnaire. Two weeks later, a questionnaire with a postage-paid self-addressed return envelope and an information brochure with general and background information about CRC and CRC screening were sent. All non-respondents received a reminder after 4 weeks, this time interval was chosen based on the literature and earlier experiences.[20–22] The mean duration between the screening examination and completion of the questionnaire was 25 months.

Questionnaire

The Integrated Model for Behavioural Change served as a theoretical framework for the development of the questionnaire; assessing predisposing, information, awareness, motivation factors and barriers that determine intention and action.[23] An extensive literature review was conducted to identify factors influencing the decision to undergo cancer screening, searching Pub-Med up to April 2008; and using the search terms '(participation OR non-participation OR non-response) AND cancer screening'. Predisposing factors assessed were behavioural (smoking, alcohol consumption, physical activity, BMI and yearly GP visits); biological (age, gender, health status and abdominal complaints); social (education, employment, income, marital status and household) and cultural (ethnicity). Health status was measured by the SF-12[24], EQ-5D[25], and a summary

Figure 1 Study flow chart; all the numbers refer to the number of questionnaires



CRC: colorectal cancer; FOBT: faecal occult blood test; gFOBT: guaiac-based FOBT; FIT: faecal immunochemical test; FS: flexible sigmoidoscopy

Excluded from the analysis:

[a] individuals that met the exclusion criteria for the population screening programme (history of inflammatory bowel disease or CRC; severe or terminal disease or a colonoscopy, double contrast barium enema or FS within the previous three years).

[b] invitees registered as non-participants who indicated that they did participate, but the test got lost in the mail.

[c] individuals who reported as their primary reason for non-participation that they never received a screening invitation.

[d] individuals who reported as their primary reason for non-participation that they were abroad for a long time.

score on a visual analogue scale (VAS). The physical (PCS) and mental (MCS) component summary measures of the SF-12 are scored using norm based methods (mean and standard deviation (SD) 50 and 10 respectively in the general US population).[26] Perceived personal CRC risk (percentage), anticipated regret, social influences, occurrence of CRC among acquaintances and endoscopy experience were assessed. Barriers and facilitators addressed included gender of the endoscopist and expected/experienced burden throughout the screening procedure of FOBT and FS. To this aim, respondents evaluated how burdensome they experienced/regarded several aspects of the screening procedure (e.g. time the FOBT/FS takes; waiting on the test results) on a five-point pre-defined scale (ranging from 1: very burdensome to 5: not burdensome at all). They were asked to rate the overall burden of the screening procedure on a scale from 1 to 10.

All relevant factors were related to both actual participation (as observed in the screening trial) and to the intention to participate in a next screening round. This intention was assessed in all groups for both FOBT and FS by a question with five response options: 'definitely'/'probably'/'maybe'/'probably not'/'definitely not'. Furthermore, in a separate question the main reason for (non-) participation was assessed.

For assessing informed choice we measured knowledge and attitudes towards CRC screening, and applied the concept Marteau developed for prenatal screening[27]: a choice based on relevant knowledge while the decision makers attitudes are consistent with her actual screen behaviour, thus characterised by having relevant knowledge and either positive attitudes and participation or negative attitudes and no participation. Knowledge was assessed through six questions on symptoms and risk factors and six questions on knowledge of benefit of CRC screening. Sufficient knowledge was defined as at least four out of six most relevant items correctly answered. The correct answers to the questions were not provided to participants. Attitudes towards CRC screening were measured by an attitudes scale based on the Theory of Planned Behaviour[28] and adapted from Marteau's multidimensional measure for informed choice.[27] It contained 10 items scored on a five-point scale, e.g. I consider undergoing CRC screening reassuring-not reassuring. Scores were transformed to a scale ranging from 0 to 100: scores below 45 indicate negative; 45–55 neutral and above 55 positive attitudes towards CRC screening.

Knowledge and attitudes were also separately related to screening intention and participation.

To measure attitudes towards preventive health care measures in general, respondents were asked to indicate of a list of preventive interventions whether they would recommend those to eligible groups, for example flu shots for the elderly.

We conducted a pilot study (n = 20) to examine whether respondents could manage the length of the questionnaire and to examine the acceptability and validity of the questionnaire. Following the pilot study, changes were made in the question order and the formulation of several questions.

Statistical analyses

Since the sample for the questionnaires was stratified for SES and sex to ensure sufficient data for both genders and all socio-economic groups, a complex samples approach was adopted, weighting the data for the gender and SES distribution in the group from which the sample was drawn. Characteristics of the different groups were compared using parametric and non-parametric tests. For categorical data, we used Pearson-Chi-square and Fisher Exact Test to test for differences between groups. For ordinal data, we used Mann Whitney *U*. For continuous variables, we used the Independent Samples *T*-Test or Mann Whitney *U*. For identifying the factors influencing actual participation and the willingness to participate in a subsequent screening round, univariate and multivariate logistic regression models were fitted. Separate models were fitted for FOBT (either gFOBT or FIT) invitees and FS invitees. To identify factors influencing the intention to participate in a next screening round, a model was fitted including all respondents to the questionnaire. In multivariate models, only variables with an alpha level ≥0.25 were retained. Possible interaction terms were incorporated in the logistic regression models based on reasoning.

All statistical tests were two-sided and considered statistically significant when $p < 0.05$.

Power calculation

We powered the study to detect a 0.5-point difference in expected unpleasantness of the screening test between participants and non-participants on a 5-point ordinal scale with an assumed standard deviation of 1.4, a power of 80% and a 5% level of significance. We therefore aimed to include 100 individuals per study arm. From the literature we expected a response rate of 70% among participants, 25% among non-participants and 25% among screening-naïve individuals.[21,29–31]

Ethical approval

The Dutch National Health Council (PG/ZP2.727.071) approved the screening trial. The questionnaire study was approved by the Institutional Review Board of the Erasmus MC (MEC-2009-326).

RESULTS

A total of 4414 questionnaires were sent (see Figure 1). The response rates differed considerably between groups, ranging from 17% to 76%, with the lowest response rates amongst non-participants. The baseline characteristics of the respondents to the questionnaire are shown in Table 1.

Table 1 Baseline characteristics of respondents

	CRC SCREENING INVITEES					Screening naïve
	FOBT participants	**FOBT non-participants**	**FS participants**	**Declined FS, accepted FOBT**	**Declined FS and FOBT**	
Respondents	230	287	111	143	167	192
Gender (male; n - %)	123 (54)	141 (49)	57 (51)	71 (50)	80 (48)	91 (47)
Age (median ± IQR)	63.5 ± 10.3	60.5 ± 9.3	63.8 ± 10.2	62.3 ± 9.1	61.8 ± 9.6	61.1 ± 8.8
Country of birth (n - %)*						
The Netherlands	217 (95)	265 (94)	104 (94)	131 (94)	142 (88)	168 (88)
Education (n - %)*						
Elementary	22 (10)	16 (6)	5 (5)	10 (7)	16 (11)	8 (4)
Secondary	120 (55)	140 (52)	57 (54)	78 (56)	78 (51)	75 (39)
Tertiary and postgraduate	76 (35)	113 (42)	44 (42)	51 (37)	58 (38)	106 (56)
Employment status (n - %)*						
Pensioner/early retirement	108 (48)	79 (28)	61 (55)	65 (47)	63 (39)	76 (40)
In paid work	82 (36)	140 (50)	39 (35)	56 (40)	74 (46)	90 (47)
Unemployed	36 (16)	60 (22)	11 (10)	18 (13)	24 (15)	26 (14)
Health Status (SF-12; mean ±SD)						
Physical health	49.8 ± 8.9	51.2 ± 8.4	49.2 ± 9.7	49.8 ± 9.0	50.7 ± 9.0	50.8 ± 8.9
Mental health	53.3 ± 8.5	52.7 ± 9.5	53.1 ± 9.4	53.6 ± 8.8	52.7 ± 9.6	53.7 ± 9.3
Sufficient knowledge of CRC and CRC screening (n - %)*	194 (87)	224 (79)	94 (85)	122 (85)	116 (74)	160 (84)

* As not all respondents completed these questions, the percentages mentioned for these items are not based on the total number of respondents, but on the total number of respondents who answered those questions.
IQR; *Interquartile range*

FOBT and FS invitees characteristics and main reasons for (non-) participation

FOBT participants versus FOBT non-participants

Compared to FOBT participants, FOBT non-participants more often completed tertiary education and were more often in paid work (Table 1). The main reasons for participation in FOBT screening were acquiring certainty about CRC presence or absence and possibility of early CRC/adenoma detection (Table 2). The main reasons for non-participation were the absence of abdominal complaints and fear that CRC is found.

FS participants versus 'Declined FS, accepted FOBT' and 'Declined FS and FOBT'

Those who declined both FS and FOBT had significantly less knowledge of CRC and CRC screening compared to FS participants and those who declined FS but participated with subsequent FOBT. Worries about test unpleasantness/discomfort/risks, were important reasons for non-participation in FS screening (Table 2).

Table 2 Main reason for participation and non-participation

A. Main reason for participation in FOBT and FS screening

	FOBT SCREENING PARTICIPANS				FS SCREENING PARTICIPANTS	
	FOBT participants (n=219)		Declined FS, accepted FOBT (n=131)		FS participants (n=103)	
Certainty about CRC presence or absence	38%	(1)	31%	(2)	32%	(2)
Possibility of early CRC/adenoma detection	32%	(2)	34%	(1)	36%	(1)
Watching/controlling own health	6%	(4)	11%	(3)	2%	(7)
Medical check through participation	5%	(5)	6%	(4)	12%	(3)
Contributing to science	5%	(5)	4%	(8)	3%	(5)
Fear of acquiring CRC	3%	(7)	5%	(6)	3%	(5)
Abdominal complaints	2%	(8)	5%	(6)	0%	-
Lower risk of dying from CRC	2%	(8)	0%	-	1%	(8)
Other	7%	(3)	6%	(4)	9%	(4)

(x): ranking of the reasons per group, with (1) being the most frequently mentioned reason.

B. Main reason for non-participation in FOBT and FS screening

	FOBT SCREENING NON-PARTICIPANTS				FS SCREENING NON-PARTICIPANTS			
	FOBT non-participants (n=268)		Declined FS and FOBT (n=150)		Declined FS, accepted FOBT (n=107)		Declined FS and FOBT (n=146)	
No abdominal complaints	16%	(1)	23%	(1)	19%	(3)	24%	(1)
Fear that CRC is found/not wanting to know if CRC is present	11%	(3)	5%	(7)	0%	-	4%	(8)
Lack of time	8%	(4)	5%	(7)	7%	(4)	6%	(5)
No specific reason	8%	(4)	8%	(5)	3%	(6)	2%	(9)
More important (health) problems	7%	(6)	10%	(4)	3%	(6)	10%	(4)
Aversion of performing test	7%	(6)	5%	(7)	2%	(8)	5%	(7)
Forgot	6%	(8)	1%	(11)	0%	-	1%	(10)
Worries about test unpleasantness/ discomfort/risks	6%	(8)	12%	(3)	38%	(1)	23%	(2)
Test difficult to perform	6%	(8)	1%	(11)	n.a.	-	n.a.	-
Fear of possible follow-up colonoscopy	6%	(8)	2%	(10)	0%	-	0%	-
Fear of participating in CRC screening	5%	(12)	6%	(6)	6%	(5)	6%	(5)
Other	14%	(2)	22%	(2)	22%	(2)	19%	(3)

(x): ranking of the reasons per group, with (1) being the most frequently mentioned reason.

CRC, colorectal cancer; FOBT, faecal occult blood test; FS, flexible sigmoidoscopy; n.a., not addressed

Individuals' characteristics associated with actual participation and next round screening intention

Individuals' characteristics associated with actual CRC screening participation

Table 3 shows the univariate and multivariate logistic regression analyses of the variables associated with actual FOBT screening participation. In multivariate analyses, being a smoker during the last 10 years, having a physical health below average, anticipated regret and a neutral or positive attitude towards CRC screening were positive predictors of participation in FOBT screening. For FS screening, this held only for a positive or neutral attitudes towards screening.

Table 3 Factors influencing the willingness to attend colorectal cancer screening

Factors influencing..	**..actual participation**		**..participants, non-participants and screening naïve: intention to participate in a next round**	
	FOBT *(n=517)*	FS *(n=421)*	**FOBT screening** *(n=1,116)*	**FS screening** *(n=1,101)*
Gender				
Male	1	1	1	**1**
Female	1.2 (0.8-1.7)	0.8 (0.5-1.3)	1.0 (0.7-1.3)	**0.6 (0.5-0.8)***
Age				
50-59	1	1	1	1
60-64	1.3 (0.8-2.1)	1.6 (0.9-2.7)	1.1 (0.8-1.6)	1.4 (1.0-1.9)*
65-74	2.2 (1.4-3.3)*	1.6 (0.9-2.7)	1.1 (0.8-1.6)	1.3 (1.0-1.7)
Socio-economic status				
Low	1	1	1	1
Intermediate	0.8 (0.5-1.1)	1.3 (0.8-2.1)	0.9 (0.6-1.2)	0.9 (0.7-1.2)
High	0.8 (0.5-1.3)	1.1 (0.6-2.0)	0.7 (0.5-1.0)	0.7 (0.5-1.0)*
Education				
Elementary	1	1	1	1
Secondary	0.6 (0.3-1.3)	2.0 (0.7-5.5)	1.2 (0.7-2.1)	1.0 (0.6-1.6)
Tertiary	0.5 (0.2-0.9)*	1.8 (0.7-4.9)	1.6 (0.9-2.7)	1.0 (0.6-1.2)
Employment status				
In paid work	1	1	1	1
Retired/ Unemployed	1.7 (1.2-2.5)*	1.8 (0.9-2.2)	1.2 (0.9-1.6)	0.9 (0.7-1.2)
Marital status				
Not married	1	1	1	1
Married	1.9 (1.2-3.1)*	1.3 (0.7-2.2)	1.4 (1.0-1.9)	1.6 (1.2-2.2)
Smoked last 10 years				
No	**1**	1	1	1
Yes	**0.6 (0.4-0.9)***	0.7 (0.4-1.1)	1.0 (0.8-1.4)	1.0 (0.8-1.3)
Alcohol consumption				
No	1	1	1	**1**
Yes	1.1 (0.7-1.6)	1.3 (0.8-2.1)	1.3 (0.9-1.7)	**1.7 (1.3-2.2)***

Table 3 (continued)

Factors influencing..	..actual participation		..participants, non-participants and screening naïve: intention to participate in a next round	
	FOBT *(n=517)*	FS *(n=421)*	**FOBT screening** *(n=1,116)*	**FS screening** *(n=1,101)*
Physical health (SF-12)				
Above average	**1**	1	1	1
Below average	**1.7 (1.2-2.6)***	1.0 (0.6-1.7)	1.4 (1.0-2.0)*	1.1 (0.8-1.4)
Abdominal complaints				
No	1	1	1	**1**
Yes	1.6 (0.8-3.1)	1.1 (0.5-2.6)	4.2 (1.8-9.7)*	**3.3 (2.0-5.5)***
Knowing someone affected by CRC				
No	1	1	1	**1**
Yes	1.4 (1.0-2.1)*	1.8 (1.1-2.7)*	1.6 (1.2-2.1)*	**1.6 (1.3-2.1)***
CRC screening attitude				
Negative attitude	**1**	**1**	**1**	**1**
Neutral attitude	**7.8 (0.9-66.0)***	**2.2 (0.3-19.0)***	**2.1 (1.1-4.1)***	**2.1 (0.9-5.3)**
Positive attitude	**39.8 (5.2-305.3)***	**15.1 (2.3-100.7)***	**24.8 (13.9-44.3)***	**16.2 (7.3-36.1)***
Anticipated regret				
No	**1**	1	**1**	**1**
Yes	**5.2 (2.5-10.9)***	2.0 (0.8-4.9)	**16.7 (11.0-25.2)***	**4.3 (3.1-5.9)***
Do not know	**0.7 (0.3-2.0)**	0.6 (0.2-2.2)	**5.5 (3.6-8.9)***	**1.9 (1.3-2.8)***
Estimated personal CRC risk				
Risk 1-10%	1	1	1	**1**
Risk >10%	1.9 (1.2-3.0)*	2.0 (1.2-3.5)*	1.8 (1.3-2.5)*	**2.1 (1.6-2.8)***
Risk not known	0.9 (0.5-1.6)	0.7 (0.3-1.5)	1.4 (0.9-2.2)	**1.0 (0.7-1.4)**
Sufficient knowledge				
No	1	1	**1**	1
Yes	1.8 (1.1-3.1)*	1.6 (0.9-2.8)	**2.6 (1.8-3.6)***	1.5 (1.1-2.1)*

* Statistically significant ($p < 0.05$) in univariate analyses

Bold: Factor statistically significant ($p < 0.05$) in multivariate analyses

CRC, colorectal cancer; FOBT, faecal occult blood test; FS, flexible sigmoidoscopy

Factors influencing intention to participate in a next screening round

Of all respondents (including non-participants and the screening-naïve group), 77% intended to participate in a next screening round with FOBT and 53% with FS ($p < 0.01$). In multivariate analyses, anticipated regret, a neutral or positive attitude towards CRC screening and sufficient knowledge were significant predictors of FOBT screening intention. Male gender, alcohol consumption (compared to no alcohol consumption), having abdominal complaints, knowing someone affected by CRC, a neutral or positive CRC screening attitude, anticipated regret and a higher perceived personal risk of CRC were positive predictors of FS screening intention.

Informed choice

Eighty-one percent of all participants made an informed choice to participate in CRC screening (sufficient knowledge and positive attitudes). Of all non-participants, 12% made an informed choice in accordance with the criteria (sufficient knowledge and negative attitudes). Fifty-two percent of non-participants made uninformed choices characterised by sufficient knowledge, positive attitudes towards CRC screening but no participation (Table 4).

Table 4 Informed choice

a. CRC screening participants (n - %)

n=443		**Knowledge**	
		Sufficient	Insufficient
Attitudes	positive	**359 (81%)[a]**	54 (12%)
	neutral	20 (5%)	3 (1%)
	negative	3 (1%)	4 (1%)

b. CRC screening non-participants (n - %)

n=385		**Knowledge**	
		Sufficient	Insufficient
Attitudes	positive	199 (52%)	13 (3%)
	neutral	63 (16%)	26 (7%)
	negative	**46 (12%)[a]**	38 (10%)

Sufficient adequate knowledge: a correct answer for least 4 out of 6 knowledge questions
[a] Individuals in these categories meet the predefined criteria of an informed choice

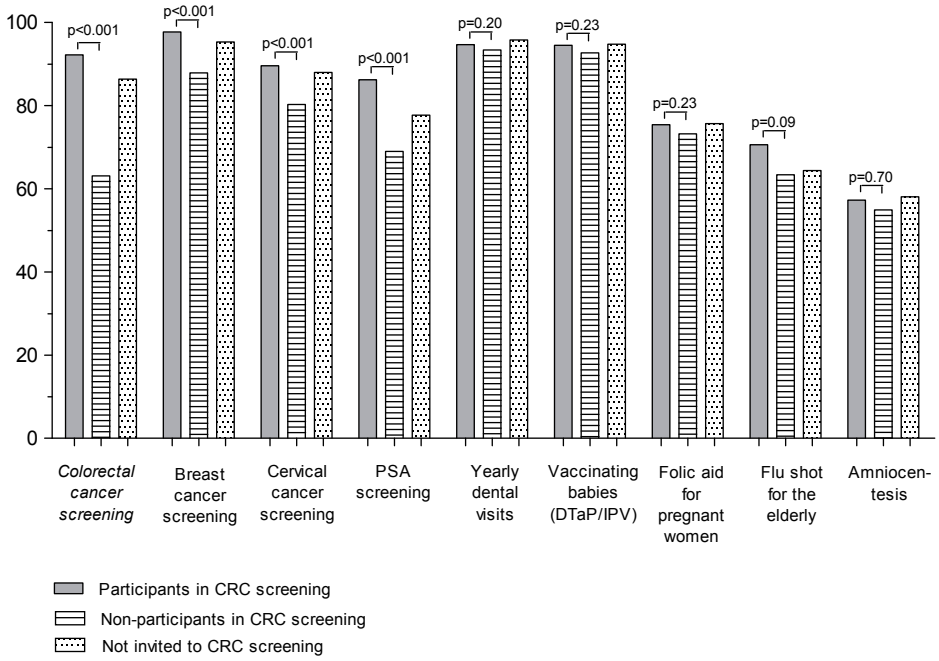
Attitudes towards preventive interventions

As expected, a significantly larger proportion of non-participants was reluctant to recommend different forms of cancer screening to those eligible compared to participants (Figure 2). However, a similar proportion of participants and non-participants recommended other preventive interventions, such as dental visits.

Differences between gFOBT and FIT screenees

The only differences between gFOBT and FIT screenees found in subgroup analyses concerned the experienced burden. gFOBT screenees experienced the time required ($p = 0.003$), waiting for the test results ($p = 0.04$) and the possibility of false-positive test results ($p = 0.03$) as more burdensome than FIT screenees. On a scale of 1–10, gFOBT participants rated the entire screening procedure lower than FIT screenees (8.08 versus 8.47, respectively; $p = 0.01$).

Figure 2 Attitude towards preventive interventions



The percentage of respondents that would recommend various preventive health care activities to eligible groups, per group and per activity. *P*-levels indicate the statistical differences between groups, assessed by logistic regression analyses, corrected for age. DTaP/IPV: Diphtheria, tetanus, whooping cough, and poliomyelitis. PSA: Prostate-specific antigen.

Actual next round screening participation

All FIT invitees, 114 FIT participants and 153 FIT non-participants, were invited for a second screening round. Fifty-seven percent of first round non-participants who intended to participate in the next screening round, did participate (Table 5).

Table 5 Second round screening participation among first round screening participants and non-participants

Intention to participate in next screening round	**Actual participation in next screening round**	All respondents combined	First round participants	First round non-participants
Yes ("Definitely" or "very likely")	Yes	133 (72%)	90 (83%)	43 (57%)
	No	51 (28%)	19 (17%)	32 (43%)
No ("Probably not" or "definitely not")	Yes	3 (15%)	-	3 (16%)
	No	17 (85%)	1 (100%)	16 (84%)
Maybe	Yes	12 (27%)	4 (80%)	8 (21%)
	No	32 (73%)	1 (20%)	31 (79%)

DISCUSSION

Our study showed that 81% of participants made an informed choice on CRC screening participation, in contrast to only 12% for non-participants. The main reason for non-participation in FOBT screening was lack of abdominal complaints; the main reasons for non-participation in FS screening were worries about the burden of the test and the absence of abdominal complaints. Anticipated regret and attitudes towards CRC screening were strong predictors of both actual participation and willingness to participate in a subsequent screening round with FOBT and FS.

To our knowledge, only one other study investigated reasons for (non)-participation among both FOBT and FS screening invitees.[32] In this Italian study, consultation of a general practitioner before undergoing screening, having a first-degree relative with CRC, regular physical activity and reading the information brochure were associated with higher attendance. In line with these findings, we found that having acquaintances affected by CRC increased screening participation, although in our study physical activity did not influence participation. In the Italian study, people who considered screening to be ineffective, those expressing anxiety and those familiar with CRC screening tests were less likely to participate. We found that attitudes towards CRC screening strongly correlated with participation. A significant proportion of non-participants reported fear for either CRC screening in general, finding CRC or the possible follow-up colonoscopy as the main reasons for non-participation.

Previous research has indicated that CRC screening participants are more often engaged in other health-promoting interventions, such as regular dental visits and other forms of cancer screening.[33–35] Also in our study, CRC screening participants had significantly more positive attitudes towards all forms of cancer screening than non-participants, but attitudes towards other preventive interventions such as interventions with regard to flu vaccination were similar.

In contrast with our hypothesis, we found that a physical health below average was a positive predictor of FOBT screening participation. A possible explanation may be that those of worse physical health may worry more about their health or are more familiar with health care and therefore are more inclined to participate.[36]

In our study, 81% of participants made an informed choice on screening participation, in contrast to only 12% of non-participants meeting the criteria for informed choice. Fifty-two percent had sufficient knowledge and a positive attitude but did not participate, suggesting that for those individuals barriers such as time-requirements, more important (health) problems or fear played a role in non-participation. While not

all of these factors may be modifiable, anxiety is a factor that may be influenced by information provision. Also, tools such as risk calculators may enhance informed decision making about uptake of screening.[37] In 20% of non-participants knowledge

was insufficient, so this group might benefit from interventions aimed at increasing knowledge. In previous research, the presence of abdominal complaints was frequently found to be associated with participation in CRC screening.[33–35,38] In our study absence of abdominal complaints was indicated as one of the main reasons for non-participation, and the presence of abdominal complaints was significantly associated with intention to participate in FS (multivariate analyses; Table 3). Knowledge of CRC and screening is a positive predictor of participation.[34,39]

Our study showed that knowledge of CRC and CRC screening was especially low amongst individuals who had declined both FS and subsequent FOBT. The explanation for this correlation may be twofold: individuals may not participate as a result of insufficient knowledge or those having participated may have more knowledge due to participation and reading the information material. The fact that the absence of abdominal complaints is the main reason for non-participation in FOBT screening, and that insufficient knowledge significantly correlates with non-participation highlights the need of adequately informing the target population, including making individuals aware that CRC symptoms mostly occur late in the course of the disease and CRC can be present without symptoms. It should be kept in mind that this trial was a first screening round in a population not familiar with CRC screening. However, it does highlight the importance of adequate information provision to the target population, as the room for improvement is considerable. So, screening organisations should focus on adequate information provision to the target population by for example suitable information brochures, information meetings, and media coverage, as this will affect the two of the most important parameters for the success of screening: informed choice and participation.

When comparing anticipated and actual participation in a next round, we found that the concordance between intention and action was better for first round participants than for first round non-participants. Overall 40% of first round non-participants who responded to the questionnaire participated in the second round, which is much higher than the overall participation rate observed among non-participants of the first round in second screening round (16–21%).[18] Probably, completing the questionnaire may have triggered awareness on CRC screening participation; resulting in a higher participation rate. Another explanation is that mainly non-participants with a positive attitude towards screening returned the questionnaire.

The main limitation of this study is the low response rate in non-participants, especially in those that declined both FS screening and subsequent FOBT screening. This may be explained by the fact that they were already contacted multiple times regarding CRC screening participation (invitations and reminders for both FOBT and FS screening). We therefore tested for differences on age, gender and SES between those who did and did not return the questionnaire (data not shown). For the groups with the lowest response rates (FOBT non-participants, those who declined FS but accepted subsequent

FOBT and those who declined both FS and FOBT) there were no significant differences on those parameters between individuals who did and those who did not return the questionnaire. However, they may have differed on other variables that we are unable to measure in the group of non-respondents to the questionnaire. The response rate in the screening naïve group was similar to other studies in the general population in the same area.[21,29] Secondly, we used the aggregate data per postal code area (small neighbourhoods) to estimate the participant's SES. An important limitation is the fact that aggregate data on SES may provide an inaccurate representation of the true individual SES. The limitations of this approach have been widely studied, with one of the most recent studies concluding that the agreement between individual level and aggregate-level SES may depend on the patient income and patient group.[40] However, 37% of the respondents to our questionnaire was not willing to complete the question on income. Our experience with questionnaire studies previously conducted in the same population is that respondents are reluctant to provide data on income. At last, we included a screening-naïve group to have a 'baseline' value among the target population; to compare all other groups to. However, the screening-naïve group was better educated than the other groups and the willingness to participate in FOBT and FS screening was very high (93% and 74% respectively would 'definitely' or 'most likely' participate); much higher than the participation rates observed in our pilot screening programmes.[13,18] This suggests a response bias among the screening-naïve group.

In conclusion, absence of abdominal complaints is an important reason for non-participation in CRC screening, implying that knowledge about CRC screening is insufficient. As a result, only 12% of non-participants had made an informed choice on non-participation. Actual and future CRC screening participation were mainly associated with anticipated regret and attitudes towards CRC. As CRC screening is introduced in many countries worldwide, it is especially important to provide great effort in informing the eligible populations about CRC screening, enabling informed decisions about uptake.

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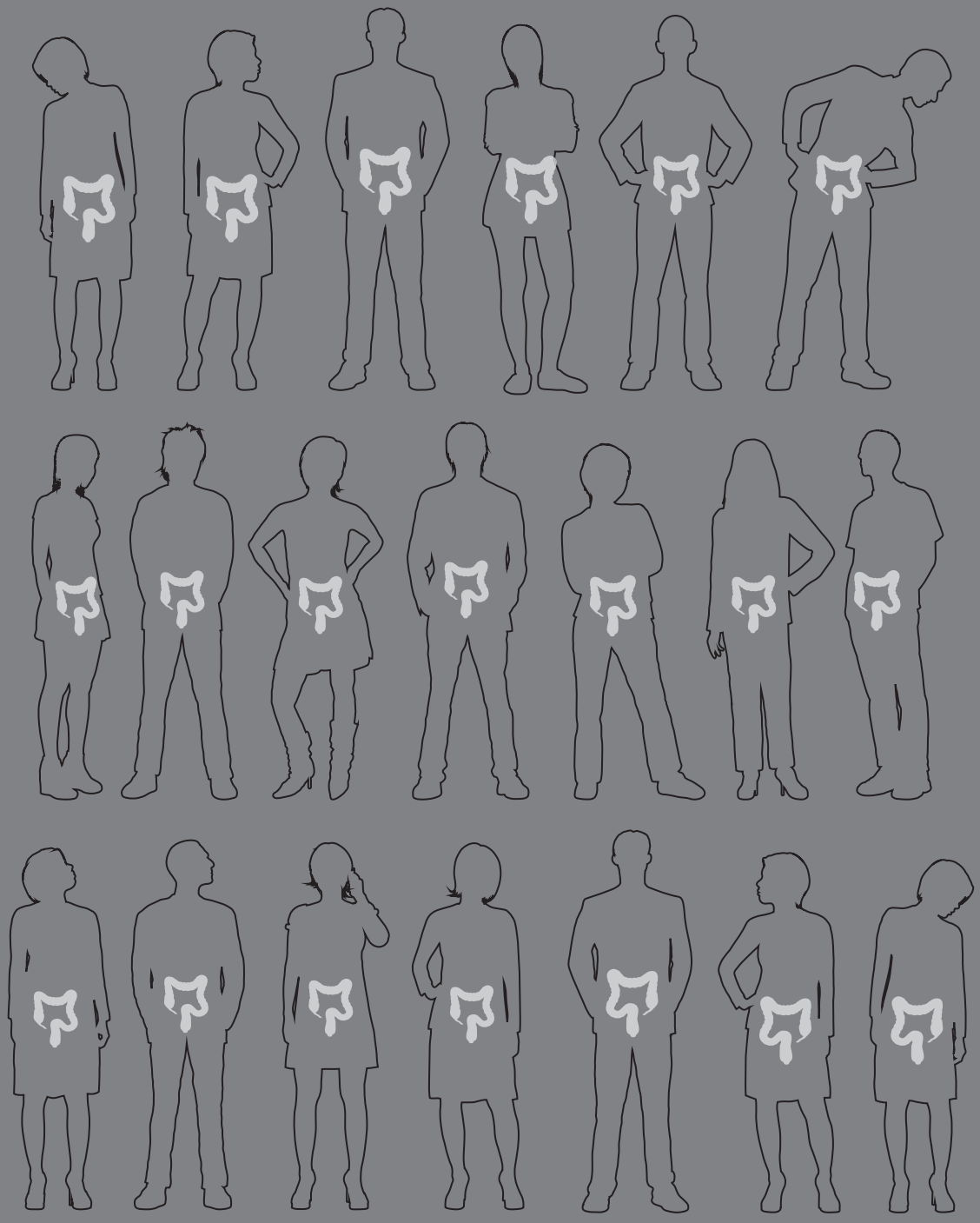

CHAPTER 5

Time requirements and health effects of participation in colorectal cancer screening with colonoscopy or computed tomography colonography in a randomized controlled trial

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ABSTRACT

Background and study aims: Time limitations and unwanted health effects may act as barriers to participation in colorectal cancer (CRC) screening. The aim of the study was to measure the time requirements and health effects of colonoscopy and computed tomography colonography (CTC) screening.

Patients and methods: This was a prospective diary study in a consecutive sample within a randomized controlled CRC screening trial, comparing primary colonoscopy and CTC screening for average-risk individuals aged 50–74 years. The diary ended when all screening-related complaints had passed.

Results: The diary was returned by 75% (241/322) of colonoscopy and 75% (127/170) of CTC screenees. The median interval between leaving home and returning from the examination was longer for colonoscopy (4 hours and 18 minutes [4:18], interquartile range [IQR] 3:30–5:00) than for CTC (2:30 hours, IQR 2:06–3:00; $p<0.001$). Similarly, the time to return to routine activities was longer after colonoscopy (3:54 hours, IQR 1:48– 15:00) than after CTC (1:36 hours, IQR 0:54– 4:42). The duration of screening-related symptoms after the examination was shorter for colonoscopy (11:00 hours, IQR 2:54–20:00) than for CTC (22:00 hours; IQR 5:30–47:00; $p<0.001$). Abdominal complaints were reported more frequently after CTC. Anxiety, pain, and quality of life worsened during the screening process, with no differences between the two examinations.

Conclusions: Compared with colonoscopy, CTC screening required less time and allowed screenees to return to their daily activities more quickly. In contrast, CTC was associated with a twofold longer duration of screening-related symptoms. Feelings of anxiety, pain, and quality of life scores were similar during colonoscopy and CTC screening. These results should be incorporated into cost-effectiveness analyses of CRC screening techniques.

INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent cancer in males and the second in females, with an estimated worldwide incidence of 1.2 million and 608 700 deaths in 2008.[1] Screening reduces CRC mortality by early detection of CRC and endoscopic removal of premalignant precursors of CRC.[2–6]

Colonoscopy and computed tomography colonography (CTC) are screening methods that allow visualization of the entire colon, and both have high sensitivities for CRC.[7] The main advantages of colonoscopy include the possibility of direct removal of lesions and the low frequency of screening required. One of the main disadvantages is the required bowel preparation prior to the procedure, which is often identified as the most burdensome aspect of the entire screening procedure.[8–10] CTC has more recently been introduced as a screening alternative, and is already recommended as a screening tool in one of the main American guidelines for CRC screening.[11] CTC has important advantages, such as its minimally invasive character and the possibility of limited bowel preparation.[12] Furthermore, the fact that CTC can be performed quickly and without the need for sedation and hence time to recover, has been mentioned as one of the aspects that makes CTC screening attractive.[13] However, findings on CTC do require follow-up by colonoscopy.

The time required by individuals to participate in screening may be a barrier to undergoing screening.[14–17] Measuring time requirements can contribute to quality control by providing information about practice efficiency.[18] Furthermore, participants' time requirements are important for an adequate evaluation of the cost-effectiveness of screening alternatives[19], and several guidelines recommend inclusion of patient time costs in costeffectiveness analyses.[20, 21] For CTC, patient time costs have already been included in cost-effectiveness analyses, but these time requirements were based on assumptions due to a lack of data.[22]

The aim of the current study was to determine the time required for participation in a CRC screening program using primary colonoscopy and CTC. As CRC screening involves the participation of healthy individuals, quality of life (QOL) during the screening process is an important factor to consider when evaluating screening alternatives. Therefore, the study also evaluated short-term QOL and health complaints before, during, and after screening.

METHODS

Study population

Participants already enrolled in the COCOS-trial (COlonoscopy or CT-COlonography for Screening)[23], which has been described in detail elsewhere[24], were included in the current analysis. This diary study was decided upon prior to initiation of the main study. In brief, 8844 average-risk individuals aged 50–74 years from the Amsterdam and Rijnmond region were randomly selected from the regional municipal administration registrations. They were randomized 1:1:1 and invited to participate in colonoscopy with either a pre-screening consultation in the outpatient clinic (OPC) or with a pre-screening consultation by telephone, or to undergo CTC screening with a pre-screening consultation by telephone. For clarity, the two colonoscopy arms (pre-screening consultation in the OPC and pre-screening consultation by telephone) were merged after testing for differences in baseline characteristics and the time requirements reported in this paper (no significant differences were present). Randomization was done per household (individuals within the same household were invited for the same modality) and stratified for age, sex, and socioeconomic status.

Individuals with CRC symptoms in the previous 3 months (rectal blood loss and/or changed bowel habits) were advised not to participate and instead to contact their general practitioner. Exclusion criteria included a full colonic examination in the previous 5 years (complete colonoscopy, CTC, and/or double contrast barium enema), being scheduled for surveillance colonoscopy (given personal history of CRC, colonic adenomas or inflammatory bowel disease), and a life-expectancy of less than 5 years. Additionally, for CTC, individuals who were pregnant, exposed to ionizing radiation for research purposes within the previous 12 months, and any individuals with hyperthyroidism or iodine contrast allergy were excluded.

All participating individuals received an information brochure with the invitation, containing information on the CRC screening program in general, benefits and risks of the screening examination, and follow-up in case of a positive result.

Ethical approval for the trial was obtained from the Dutch Health Council (2009/03WBO, The Hague, The Netherlands). The trial is registered in the Dutch Trial Register: NTR1829 (http://www. trialregister.nl).

Recruitment

Between 16 February 2010 and 27 May 2010, all consecutive trial participants were invited to this study on time investment at the end of the pre-screening consultation. Individuals unable to read and/or speak the Dutch language were excluded. Participants who provided informed consent were asked to complete a time diary, starting the day before the preparation for the examination and ending when they felt completely back to normal.

Consenting participants in the OPC group received information about the study and the diary during the consultation from the physician. Individuals in the telephone consultation groups received the documents by mail. Colonoscopy and CTC were scheduled within 4 weeks, unless participants wanted to be screened at a later time.

For the present analysis, the OPC and telephone consultation groups for colonoscopy were combined, as exploratory analyses revealed no relevant differences.

Examinations

Preparation for colonoscopy consisted of drinking a total of 2L of polyethylene electrolyte glycol solution (Moviprep; Norgine bv, Amsterdam, The Netherlands) and 2L transparent fluid as a split dose equally divided over the day before and the day of the examination. Intravenous midazolam and fentanyl were administered if desired. Antispasmodic medication was administered at the discretion of the endoscopist. All colonoscopies were performed by experienced endoscopists (≥1000 colonoscopies). CTC preparation consisted of two 50-mL doses of iodinated contrast agent (Telebrix, Geurbet, Aulnay sous Bois, France) on the day prior to CTC (starting at lunchtime) and 50mL 1.5 hours before the examination. Colonic distension was achieved with CO2 insufflation after intravenous administration of 1mL butylscopolamine or (when contraindicated) 1mg of glucagonhydrochloride intravenously. All CTC examinations were performed by experienced personnel.

Diary

Participants were asked to maintain a diary at several time points, from starting the preparation until they felt completely normal again.

The time of commencement and conclusion of the examination, and the time the participant left the recovery unit were recorded by staff. All other measurements were completed by the participants themselves. The diary included a health status measurement at five different time points (the day before the start of preparation, i. e. 2 days before the examination; the morning before the examination; the evening of the examination; the day after the examination; and up until the moment of feeling completely normal again). The health status measurement included general health on a five point Likert scale (excellent, very good, good, fair, and poor), a visual analog scale (0–10) for both QOL and pain, the anxiety instrument STAI-6, and a registration of health complaints. The STAI-6 assesses general anxiety; it is a validated short version of the State Trait Anxiety Inventory and contains six items such as feeling at ease or upset. Higher scores (20–80) indicate higher levels of generic anxiety[25, 26], with a score of over 44 defining an individual as highly anxious[27]. The diary also included questions on background variables and method of transportation. When completed, the diary was mailed to the study coordinator in a self-addressed, postage-paid envelope. A pilot study (n=10) was

conducted to ascertain whether respondents could manage the length of the diary and to examine its intelligibility and acceptability.

Statistical analysis

The main outcome measures were differences in time intervals between individuals undergoing colonoscopy and those undergoing CTC. Time intervals were described by median and interquartile range (IQR). No attempt was made to impute missing values, as time spent was dependent on multiple factors, which we believed could not be adequately corrected for with imputation models. Differences in time intervals between both groups were assessed using Mann Whitney U-tests. Linear regression analysis was performed to assess the relationship between time requirements and several pre-defined factors, based on reasoning and the literature[18]: sex, age (continuous), employment status (paid work "yes/no"), method of transportation, couple ("yes/no"), and general health (baseline measurement). As randomization was done per household and couples frequently requested same-day examinations, the differences between screenees who were part of a couple when both partners were participating and those with no participating partner were tested (couple "yes/no"). For the interval from the end of the examination until feeling normal again, the reported health complaints on the day after the examination (abdominal complaints, nausea, tiredness, headache, pain, QOL, STAI-6) were added to the model as possible explanatory factors.

For all health status measurements a Generalized Estimating Equations Model[28] was used, which included sex and age, and adjusted for baseline factors to ensure that the health status measurements were not influenced by baseline differences. An interaction term between test and time moment was also included to evaluate whether there were differences in the course of complaints between colonoscopy and CTC.

Statistical significance was defined as a two-sided p value <0.05. Statistical analyses were performed using SPSS PASW, version 18 (SPSS Inc., Chicago, Illinois, USA).

Sample size

This study was a sub-study within an randomized controlled trial (RCT). The sample size was calculated for the primary aim of the RCT. A formal sample size calculation for the current diary study was difficult as no data were available on time requirements for CTC. A previous study investigated screenees' time requirements for colonoscopy, and the sample size (n=110) in that study was sufficient to show differences in time requirements between subgroups.[18] These results motivated the sample size chosen for the current diary study. Alternatively, the sample size could be calculated formally, using default alpha (5 %) and beta (20 %) settings: an effect size of at least 0.4 SD (Cohen's d) with 80% power would require a sample size of at least 100 individuals per arm.

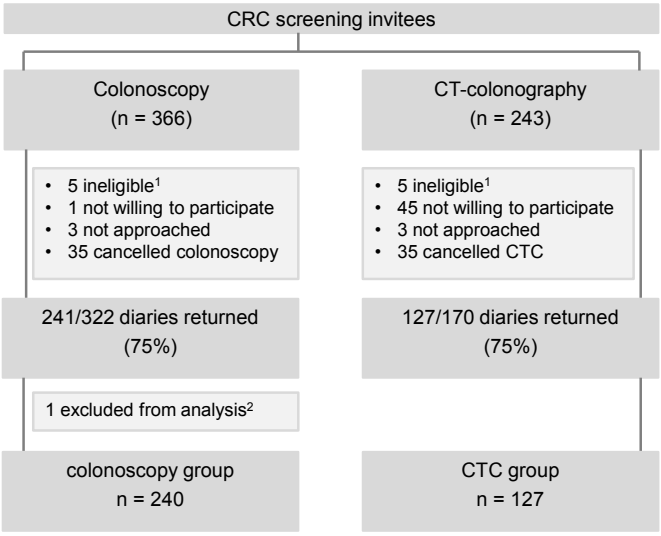
The aim was to include 130 individuals per arm, to guarantee enough analyzable data, assuming that some diaries would be completed erroneously. Based on the power analysis, not all of the 2258 participants of the RCT were approached[23], instead a consecutive sample of at least 130 subjects was invited for each group. The sample was a consecutive sample to minimize selection bias.

RESULTS

Overall, 241/322 (75 %) of eligible colonoscopy and 127/170 (75 %) of eligible CTC screenees returned their diaries (Figure 1). There was a greater number of colonoscopy screenees due to the merging of both colonoscopy arms (see *Methods* section). The sample was 50% male, mostly of Dutch ethnicity (98 %), and about 50% of participants were currently employed. Baseline characteristics of both groups were similar (Table1), except that more colonoscopy screenees were part of a couple where both partners participated.

Of colonoscopy screenees, 210 (88 %) received premedication; 17 (7 %) fentanyl and 193 (80 %) fentanyl and midazolam. The dose of midazolam was 2.5–5mg in 93% of cases, and the dose of fentanyl was 0.05mg in 92%. Butylscopolamine was administered

Figure 1 Study flow chart



CRC, Colorectal cancer; *CTC*, CT-colonography

[a] Individuals not able to speak and/or read the Dutch language were considered ineligible and not approached for participation

[b] One colonoscopy diary was excluded since the subject did not undergo colonoscopy due to vasovagal syncope prior to the examination

Table 1 Baseline characteristics

	Colonoscopy	CT-colonography
Diaries	240	127
Gender (male; n - %)	124 (52)	61 (48)
Age (median ± IQR)	60.2 ± 9.7	60.3 ± 10.1
Dutch ethnicity (n - %)	235 (98)	124 (98)
Socio economic status (n - %)		
High	99 (41)	48 (38)
Intermediate	58 (24)	34 (27)
Low	83 (35)	45 (35)
Education (n - %)*		
Elementary	6 (3)	5 (4)
Secondary	131 (55)	73 (58)
Tertiary and postgraduate	93 (39)	48 (38)
Employment status (n - %)*		
In paid work	115 (50)	63 (50)
Unemployed	41 (18)	19 (15)
Pensioner/early retirement	75 (33)	40 (32)
Married or living together (yes; n - %)*	211 (88)	103 (81)
Part of couple of which both participate (yes; n-%)	122 (51)	48 (38)

IQR, Interquartile range

* Since not all respondents completed the questions on their education, marital status and employment status, the percentages mentioned for these items are based on the total number of participants who answered those questions.

to 50% of colonoscopy screenees. For CTC, butylscopolamine was administered in 61% and glucagonhydrochloride in 38%; sedation was not administered.

Time requirements

There were five implausible extreme values regarding the interval from starting the preparation until leaving home (≥48 hours), and two in the time from leaving the recovery (colonoscopy)/end of examination (CTC) until arriving back home (≥4 hours; these individuals indicated that they first went to work after the examination, and they erroneously included this time in travel time until arriving home). These extreme values were excluded.

The median time requirements for the different aspects of colonoscopy and CTC screening are presented in Table 2. The median time between leaving home for the examination and returning to routine activities was 6 hours (IQR 4–17 hours) for colonoscopy and 3 hours (IQR 2–6 hours) for CTC. The median total time invested in the screening process, from starting the preparation until feeling back to normal was significantly shorter for colonoscopy (35 hours, IQR 22–39) compared with CTC (43 hours, IQR 26–67; $p<0.001$).

Table 2 Time intervals for colonoscopy and CT-colonography screening (CTC)

	Colonoscopy	CTC	p-value
Start preparation (Moviprep/Telebrix) until leaving home	16:36 hrs (14:48 – 18:12 hrs)	18:48 hrs (18:18 – 19:30 hrs)	$p<0.001$
Leaving home until arriving in the hospital	30 min (30 - 47 min)	30 min (25 - 43 min)	$p=0.05$
Arriving in the hospital until start of the examination	1:08 hrs (44 min – 1:28 hrs)	35 minutes (18 - 25 min)	$p<0.001$
Examination	21 min (16 – 28 min)	20 min (18 - 25 min)	$p=0.62$
Recovery time (colonoscopy only)	56 min (34 min – 1:10 hrs)	-	-
Leave recovery unit (colonoscopy)/End of the examination (CTC) until returning home	1 hr (45 min – 1:29 hrs)	52 min (38 min – 1:11 hrs)	$p=0.03$
End examination until returning to routine activities	3:54 hrs (1:48 - 15 hrs)	1:36 hrs (54 min – 4:42 hrs)	$p<0.001$
End examination until feeling completely back to normal	11:18 hrs (2:54 – 20:18 hrs)	22:18 hrs (5:30 – 46:30 hrs)	$p<0.001$

Hr, Hour; *hrs*, Hours*; min*, Minutes
Time requirements shown as either minutes or hours:minutes (e.g. 1:06 hours equals one hour and six minutes). All intervals are presented as median (interquartile range).

Factors influencing time requirements

The variables influencing the time requirements are shown in Table3. The duration between the end of the examination and feeling completely normal again was only related to the presence of abdominal complaints on the day after the examination (with the health status measurements on the day after the examination added to the model as explanatory variables): for those with abdominal complaints, median 35 hours (IQR 17–69 hours), and for those without complaints, 9 hours (IQR 3–20 hours; $p<0.001$).

Health status measurements

Abdominal complaints were reported on at least one time point by 52% of colonoscopy screenees compared with 85% of CTC screenees ($p<0.001$), tiredness by 30% and 34% ($p=0.40$), headache by 27% and 20% ($p=0.20$), and nausea by 21% and 18% ($p=0.60$), respectively (Figure 2). Taking into account baseline factors, abdominal complaints were reported more frequently during the screening process by CTC screenees ($p<0.001$), with no differences regarding other health complaints or experienced pain. Overall, there were no differences in QOL scores between colonoscopy and CTC screenees ($p=0.85$). For both groups combined, the QOL was significantly reduced on the evening of the examination compared with the baseline measurement ($p<0.001$). When feeling completely normal again, QOL was significantly increased compared with the baseline measurement ($p<0.01$). Anxiety scores were somewhat lower for colonoscopy than for CTC screenees (30 and 31 respectively; $p=0.04$), and were significantly reduced for both tests when feeling completely normal again compared with baseline.

Table 3 Time-requirements for different subgroups (colonoscopy and computed-tomographic colonography (CTC) combined)

		Preparation (until leaving home)	Travel time to the hospital	Waiting time in hospital before examination	Examination	Recovery time (colonoscopy only)	Travel time back home*	Returning to routine after examination	Feeling back to normal after examination
Sex	Male	18 hrs (15-19hrs)	30 min (25-45 min)	58 min (35min-1:26 hrs)	20 min (17-26 min)	56 min (35 min-1:06 hr)	56 min (35min-1:16 hrs)	2:21 hrs (1:17-7:53 hrs)	14:42 hrs (2:44-23 hrs)
	Female	18 hrs (16-19 hrs) [a]	30 min (30-45 min) [a]	54 min (35-1:13 hrs) [a]	20 min (17-28 min) [a]	60 min (40 min-1:11 hrs) [a]	60 min (42min-1:29 hrs) [a]	3:29 hrs (1:20-11 hrs) [a]	17:26 hrs (4:19-28 hrs) [a]
Age**	<60	18 hrs (15-19 hrs)	30 min (25-45 min)	51 min (35 min-1:14 hrs)	21 min (17-27 min)	56 min (38 min-1:05 hrs)	60 min (40 min-1:30 hrs)	2:52 hrs (1:17-7:33 hrs)	16:24 hrs (3:10-32 hrs)
	>60	18 hrs (16-19 hrs) [b#]	30 min (24-45 min) [b]	60 min (35 min-1:25 hrs) [b]	20 min (17-27 min) [a]	60 min (40 min-1:10 hrs) [b]	60 min (40 min-1:17 hrs) [a]	3:09 hrs (1:19-13 hrs) [a]	16:24 (3:14-22 hrs) [a]
Mode of transport	Car/taxi	18 hrs (16-19 hrs)	30 min (25-40 min)	51 min (35 min-1:14 hrs)	20 min (17-27 min)	59 min (34 min -1:06 hr)	56 min (39 min -1:15 hr)	3:03 hrs (1:16-10 hrs)	16:35 hrs (3:15-26 hrs)
	Public transportation	17 hrs (16-19 hrs) [a]	1 hour (45 min-1:40 hrs)[d#]	1:12 hr (57 min -1:29 hrs)[c#]	20 min (16-25 min) [a]	1:05 hr (52 min – 1:24 hr)[d#]	1:29 hr (57 min-1:57 hr) [d#]	3:26 hrs (1:38-15 hrs) [a]	16:11 hrs (3:05-22 hrs) [a]
Participating as…	..individual	18 hrs (16-19 hrs)	30 min (25-45 min)	44 min (30 min -1:13 hrs)	21 min (18-26 min)	60 min (39 min-1:05 hrs)	50 min (35 min-1:11 hrs)	2:46 hrs (1:14-11 hrs)	17:56 hrs (3:09-39 hrs)
	..couple	18 hrs (15-19 hrs) [a]	30 min (25-45 min) [a]	1:03 hrs (40 min-1:25 hrs) [c#]	20 min (16-29 min) [a]	60 min (38 min-1:15 hrs) [a]	1:04 hrs (47 min-1:35 hrs)[d#]	3:17 hrs (1:31-8:43 hrs) [a]	15:32 hrs (3:19-22 hrs) [a]

Hr, Hour; *hrs*, Hours*; min*, Minutes

Time requirements shown, depending on the magnitude, as either minutes, hours or hours:minutes (e.g. 1:06 hours equals one hour and six minutes).

All intervals are presented as median (interquartile range).

* travel time back home leaving recovery unit for colonoscopy screenees/end of the examination for CTC screenees

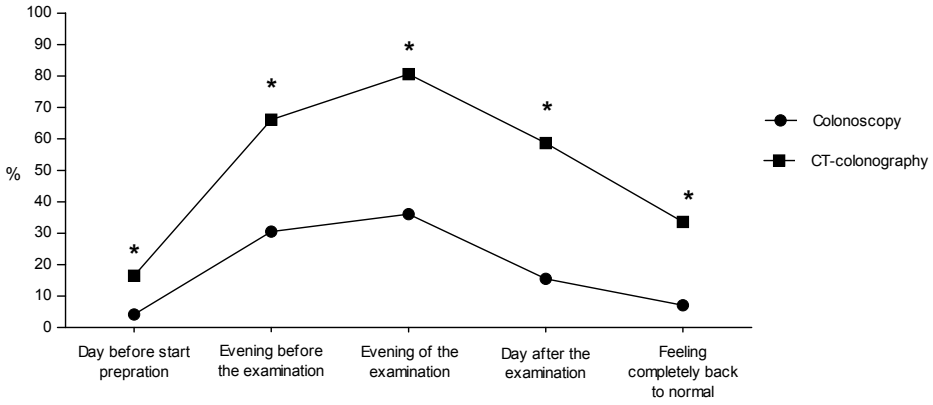
***p*-values for age based on logistic regression analysis with age as a continuous variable.

p-values based on univariate logistic regression analysis: [a]=No significant difference between both groups in logistic regression analysis; [b]= $p<0.05$; [c]=$p<0.01$; [d]=$p<0.001$

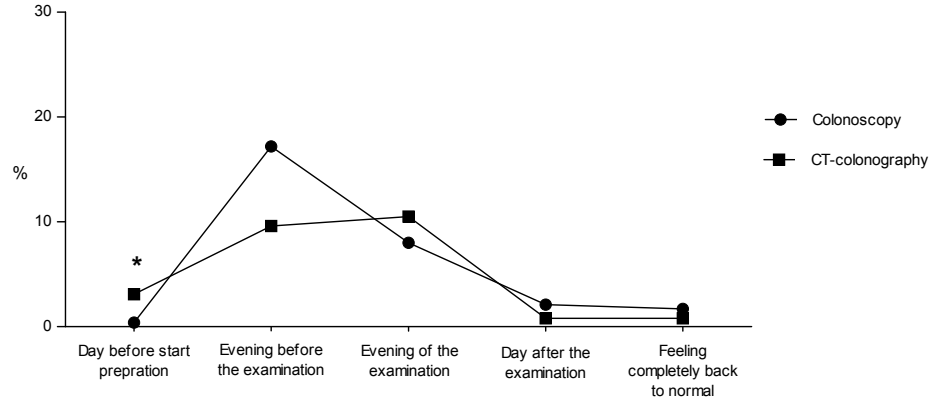
[#] = Factors that remained significant in multivariate analysis

Figure 2 Health complaints during screening participation in 239 participants in colonoscopy screening and 127 participants in CT-colonography screening

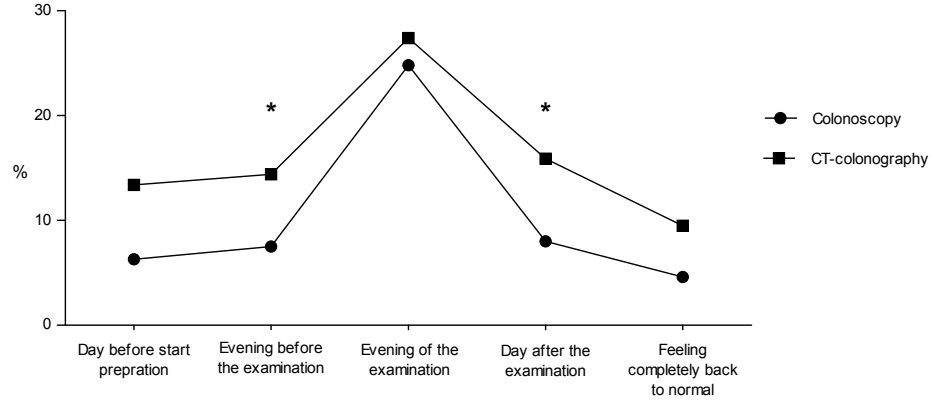
a: Abdominal complaints



b: Nausea



c: Tiredness



**Difference between colonoscopy and CT-colonography screenees: p-value<0.05*

DISCUSSION

This study investigated the time required for and the effects on experienced health of primary colonoscopy and CTC screening, within a population-based randomized controlled screening trial. The time between leaving home for the examination until returning to routine activities was significantly shorter for CTC than for colonoscopy. The time it took to feel completely normal again was considerably longer following CTC than after colonoscopy. With the exception of abdominal complaints, which were reported more frequently by CTC screenees, there were few differences in experienced health between the two screening groups.

The study has several strengths. The study recruited consecutive screenees within a randomized controlled screening trial, thereby minimizing selection bias. Furthermore, the screening-naïve individuals were directly selected from the population registry without any pre-selection criteria, making the results representative for the Dutch population. The response rate to the diary was high (75% in both groups).

The study also has some limitations. First, participation in colonoscopy in the screening trial was lower than participation in CTC screening (22% vs. 34%)[23], which may have influenced the results. A significantly larger proportion of CTC than colonoscopy participants reported abdominal complaints (4% vs. 17%) on the baseline measurement. Although this difference was corrected for by applying a generalized estimating equations model, this finding may suggest that individuals who are familiar with abdominal complaints may be more inclined to participate in CTC screening than in colonoscopy screening, therefore resulting in a selection bias. Furthermore, the phrase "feeling completely normal again" is subject to expectations about the procedure and therefore introduces subjectivity to the results. Individuals may interpret "completely back to normal" differently, as confirmed by the finding that some measurements had not returned to baseline values when individuals indicated that they were feeling completely normal again. We feel it is unlikely that this fully explains the differences between both groups, as the diaries of colonoscopy and CTC screenees were identical on this point. The pilot study revealed no difficulties regarding this matter. The results may not be unconditionally generalizable to patients undergoing colonoscopy or CTC outside the context of screening; for example, due to the fact that many couples participated, the time spent in the screening unit was likely overestimated as individuals waited for their partners. Finally, the time required for colonoscopic follow-up of a positive test result on CTC was not measured. This may be different from a primary screening colonoscopy due, for example, to logistical differences.

To our knowledge, this is the first study to directly compare the time requirements and the health experienced during colonoscopy and CTC for CRC screening. A previous study from the USA that investigated time requirements for screening colonoscopy only,

found that the median time between starting the preparation and feeling completely normal again was 40 hours compared with 35 hours in the current study.[18] The interval before returning to routine activities (16 hours after arriving back home) also seems longer than the interval in the current study. The interval between returning to routine activities and feeling normal again was much shorter in the American study. The studies used exactly the same definition of returning to routine activities and feeling completely normal again, so it is unclear how this difference may be explained. There might be differences in the time schedule for starting the preparation, explaining the difference in total time. Two Canadian studies, with a focus on nonmedical costs of CRC screening[29,30] found a somewhat shorter travel time, and a longer time spent in the clinic for colonoscopy and CTC compared with the current findings. However, the method of data collection and exact time points recorded differed between the studies.

In the current study the duration to feeling completely normal again was unexpectedly longer for CTC screenees. When looking further at factors that may explain this difference, a multivariable analysis found the presence of abdominal complaints on the day after the examination to be significantly related to the time it took to feel normal again. This might be due to the bowel preparation used; Telebrix is a non-cathartic iodine-based bowel preparation, and several CTC screenees reported having diarrhea for several days after the examination. A previous study reported that nearly all CTC screenees reported diarrhea after using noncathartic iodine-based bowel preparation.[12] So, the time before feeling completely normal again may be longer mainly due to the abdominal complaints caused by the preparation for CTC. Non-cathartic bowel preparation is a relatively new and promising alternative to the currently used cathartic bowel preparations, although it is not currently recommended as there is no evidence from direct comparative studies regarding diagnostic accuracy.[23, 31] For future research, it would be interesting to compare the influence of both preparations on the duration of abdominal complaints after CTC, as this may be an important aspect in determining the time required to feel completely normal again.

The finding that CTC screenees returned to their daily activities sooner is especially relevant for the comparative cost-effectiveness of colonoscopy and CTC, as a loss of productivity will be relevant in economic evaluations of screening strategies.

Screenees participating simultaneously with their partner spent more time in the hospital prior to the examination, and before returning home at the end of the examination. This may be explained by the fact that 75% of all couples had a same-day examination. One might expect that in a nationwide population screening program, couples will also make same-day appointments.

As CRC screening involves the participation of healthy individuals, a possible loss of QOL induced by screening examinations may influence decisions about screening strategies. In the current study, QOL was reduced only on the evening of the examina-

tion, after which it returned to levels above that of baseline values. Furthermore, anxiety scores were significantly improved compared with baseline. This may be explained by the reassurance felt after participation, resulting in improved QOL and re-duced anxiety. The change in anxiety may also partly be explained by the fact that the baseline measurement was on the day before the start of the preparation, at which point the prospect of participation may have already influenced anxiety levels. In summary, this study showed that both colonoscopy and CTC screening require considerable time investment from participants. Time before returning to routine was shorter for CTC than for colonoscopy, but the time required to feel completely normal again was longer for CTC screening participants. Except for abdominal complaints, there were few differences between colonoscopy and CTC screenees with respect to several aspects of experienced health during participation.

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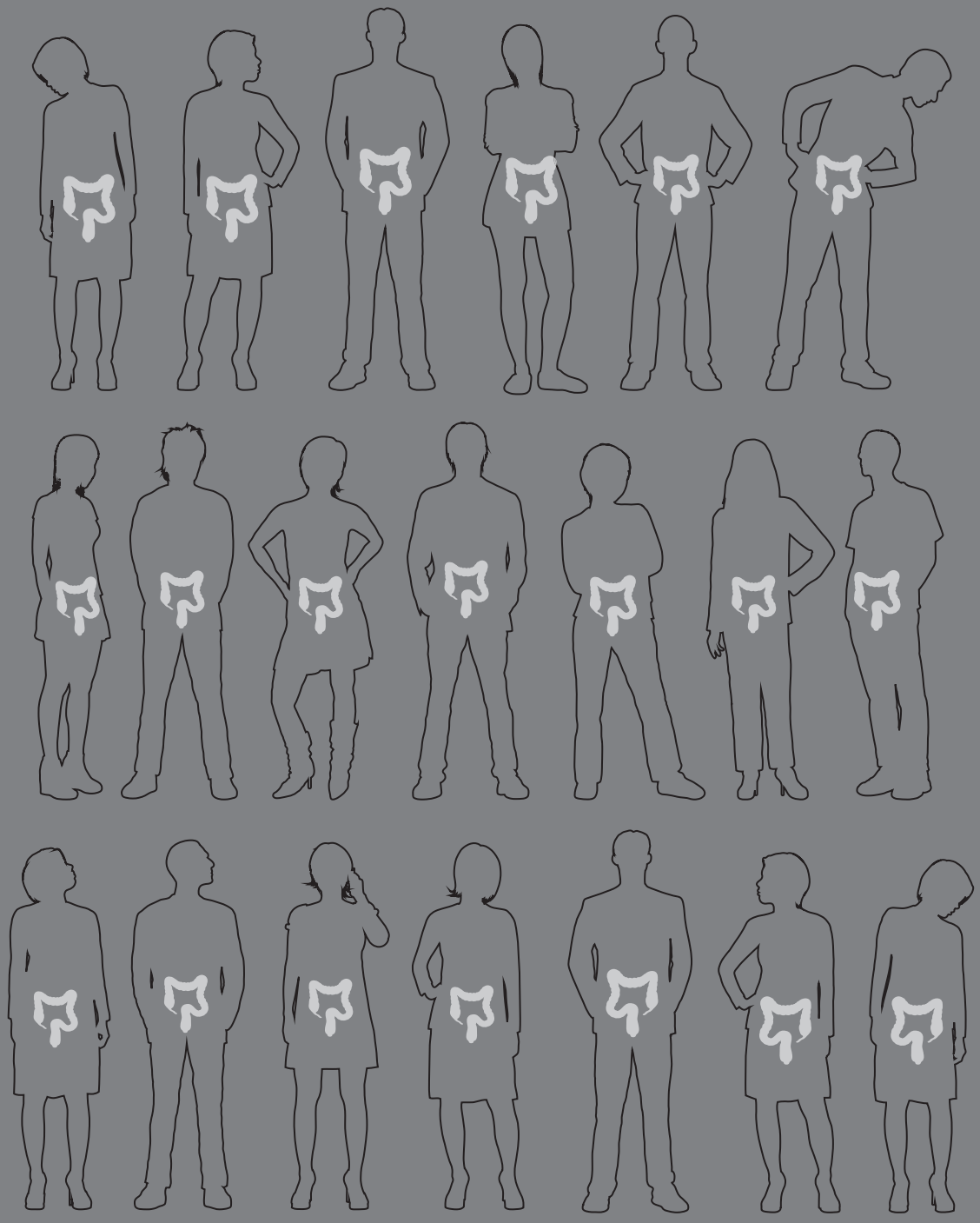

CHAPTER 6

The price of autonomy: should we offer individuals a choice of colorectal cancer screening strategies?

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ABSTRACT

A difference between colorectal cancer screening and screening for most other types of cancer is that various screening methods are available. A choice between screening methods is common in the USA. Most European programmes currently offer a single screening method, since it is recommended that only screening strategies with sufficient evidence for a reduction in colorectal cancer mortality are introduced. Faecal occult blood testing is widely accepted in Europe, and evidence on the effectiveness of flexible sigmoidoscopy is increasing. The availability of multiple effective screening options warrants deliberation on whether individuals should be given a choice between strategies. In this Personal View, we present arguments in favour and against offering a choice of screening strategies, together with the evidence substantiating these views. We also focus on screening invitees' autonomy, which is a crucial parameter in the debate.

BACKGROUND

Colorectal carcinoma is an important health problem; it is the second most common malignancy and the second leading cause of cancer-related death in developed countries.[1] The disease is characterised by a long preclinical stage, starting with the formation and slow progression of a colorectal polyp. This preclinical stage offers the opportunity for cancer prevention, by screening and treating premalignant lesions and early cancers. By contrast with most other types of cancer screening, there are several screening methods available for colorectal cancer. These screening methods can be divided into two categories: faecal tests (ie, faecal occult blood tests [FOBTs] and faecal DNA testing) and structural exams (ie, sigmoidoscopy, colonoscopy, and CT colonography; Table 1). These methods differ with respect to invasiveness and burden of the procedure, certainty for detecting colorectal cancer (related to the sensitivity and specificity of the method), required screening frequency, and features such as location of screening and handling of stool.

Colorectal cancer screening is a developing area, with worldwide variation in the preferred screening strategy. Many experts have advocated offering individuals a choice between available screening methods,[18–20] a strategy that has been advocated in the USA.[18] Although various screening strategies are recommended in the USA, allowing for patient choice,[18,21,22] in practice, physicians might promote a single strategy or only two strategies.[23] European countries often implement programmatic screening by offering a single method to the target population.[24] Of the organised colorectal cancer screening programmes in Europe in 2007,[24] five offered FOBT only, three offered flexible sigmoidoscopy only, one offered colonoscopy only, and one programme offered both FOBT and flexible sigmoidoscopy. Until 2010, FOBT was the only screening method supported by evidence from prospective, randomised controlled trials showing a reduction in colorectal cancer mortality. In particular, the guaiac-based FOBT (gFOBT) has been proven to reduce colorectal cancer mortality by about 16%,[6] and is widely recommended.[5,18,25] Since then, four randomised trials have provided evidence on the effectiveness of flexible sigmoidoscopy screening in reducing colorectal cancer mortality (Table 1).[8–11] Results of the randomised NordICC-trial (NCT00883792) and a Spanish trial[26] are expected to provide data on the effectiveness of colonoscopy screening in reducing colorectal cancer-related mortality. Population-based studies on the diagnostic accuracy of faecal DNA testing in average-risk individuals are underway.[27] Within the evolving field of colorectal cancer screening, it is important to consider whether, and on what grounds, individuals should be given a choice between screening strategies. Similar reflection will most likely be needed for other cancer types, for example breast cancer, where different screening options are becoming available. This Personal View focuses on the advantages and disadvantages of offering a single option versus a choice

of colorectal cancer screening methods, taking into con-sideration practical and ethical considerations.

METHODS

Relevant references were found through searches of PubMed, using the following keyword searches: "cancer screening AND autonomy"; "colorectal cancer screening AND preferences"; "cancer screening AND choice AND participation"; "cancer screening AND informed choice"; "sensitivity OR specifi city OR accuracy AND faecal occult blood test OR fecal occult blood test"; "sensitivity OR specifi city OR accuracy AND sigmoidoscopy"; "sensitivity OR specifi city OR accuracy AND colonoscopy"; "sensitivity OR specifi city OR accuracy AND (CT OR computed tomographic) AND colonography"; "participation AND faecal occult blood test OR fecal occult blood test"; "participation AND sigmoidoscopy"; "participation AND colonoscopy"; "participation AND (CT OR computed tomographic) AND colonography; "population screening AND colorectal cancer AND cost-eff ectiveness"; "faecal occult blood test OR fecal occult blood test AND burden"; "sigmoidoscopy AND burden"; "colonoscopy AND burden"; "(CT OR computed tomographic) AND colonography AND burden"; and "colorectal cancer screening AND "interval cancer"". Further relevant articles were identified through hand-searching of reference lists of included articles. Only articles published in English were included. There were no date restrictions.

AUTONOMY

Autonomy is a deeply rooted value in modern, developed societies. There is a distinction between autonomy as a capacity that individuals possess (which can be restricted, by mental impairment for example) and an autonomous decision.[28] Respect for autonomy has been characterised as recognising a person's capacities and perspectives, and their right to hold views and make choices based on personal beliefs.[29] Patients should be able to make autonomous decisions about their health care, although such decisions might be limited by internal and external factors such as pressures (eg, by insurance companies, family, and society), absence of adequate alternatives, and a lack of information.[28,30] Several concepts of respect for autonomy in clinical care have been defined.[31] The most widely used concept of autonomy in health care refers to the idea that patients make their own decisions, and that they are enabled to do so. Beauchamp and Childress[32] define an autonomous choice as one that occurs when people act intentionally, with understanding and without controlling influences that determine their actions, assuming that individuals are rational and reasonable agents. This definition will be used here.

Table 1 Overview of different screening methods for colorectal cancer (CRC) screening

	Faecal occult blood testing (FOBT)	Flexible Sigmoidoscopy	Colonoscopy	CT-colonography (CTC)
Nature of the test	Non-invasive, home-based	Hospital/clinic-based	Hospital/clinic-based	Hospital/clinic-based
Variants	- Guaiac-based FOBT (gFOBT) - Fecal immunochemical test (FIT)	Not applicable	Not applicable	Not applicable
Procedure	For most gFOBTs two samples from three consecutive bowel movements are collected, most FITs require collection of a single stool sample.	Preparation with an enema and fasting prior to the procedure. The last 60 centimetre of the colon are examined by means of a tube containing a video camera. In most cases performed without sedation. CRC precursor lesions (polyps) can be removed.	Prior to procedure fasting and drinking of usually 4 litres laxative fluids, therefore individuals are usually required to stay home a half-day. The entire colon is examined by means of a tube containing a video-camera. In most cases performed under conscious sedation. CRC precursor lesions (polyps) can be directly removed.	Both purgative and limited (fecal tagging) bowel preparation available. Low fibre diet required prior to procedure Radiologic examination visualising the entire colon and rectum, usually performed without sedation. Carbon dioxode is insufflated into the bowel through a small tube, in order to achieve adequate colonic distension.
Follow-up after a positive test result	Colonosocpy	Colonoscopy	None. Considered the gold standard for CRC diagnosis.	Colonoscopy
Screening frequency	Annual or biennial	Five to ten yearly	Ten yearly to once only	Five yearly
Test accuracy	Sensitivity for CRC ranges from 13-64% for gFOBT, 56-89% for FIT; with specificities of 91-95% for gFOBT and 83-97% for FIT.[2] Single test sensitivity remains relatively low, program sensitivity* is higher.[3]	One-time sensitivity of FS is estimated to be >95% for CRC in the distal colon and 30-70% for advanced adenoma.[4]	Sensitivity is assessed to be 95% for CRC and 88-98% for advanced neoplasia[4], depending on the skills of the endoscopist.	A large study with individuals undergoing same day CTC and colonoscopy assessed sensitivity and specificity for large adenomas (≥10 mm) to be 94% and 96% respectively, and for adenomas ≥6mm 89% and 80% respectively.[5]

Table 1 (continued)

	Faecal occult blood testing (FOBT)	Flexible Sigmoidoscopy	Colonoscopy	CT-colonography (CTC)
Participation rates	Uptake in population-based screening programmes 17%-90% for first round; 22%–52% in subsequent rounds.[6] Uptake is higher for FIT than gFOBT.[7]	Uptake 32-84% in RCTs (high rates in studies inviting only volunteers or those responding positively to a questionnaire determining interest in participation)[6, 8-14], 7-55% in population based programmes[6, 15-18].	18-40%; Germany 2-3% annually, cumulative 6-year participation 16-17%[10, 19-23]	Participation ranges from 16-32%.[19, 21, 24, 25]
Evidence for mortality reduction	RCTs[a] have shown that gFOBT screening reduces CRC mortality by on average 16%.[26-30] Currently no evidence for FIT, but expected to be at least equal to gFOBT based on modelling.[31]	One RCT demonstrated no effect on CRC mortality reduction after 7 years[32]. Other RCTs showed in intention-to-treat analyses that a single FS reduced CRC mortality by 31%[33], 22% (not significant)[34], and 26%[35]. In per-protocol analyses, CRC mortality was reduced by 43%[33], and 38%[34].	No data from RCTs available yet. Based on modelling, colonoscopy screening is expected to reduce CRC incidence by 76-90%[36] and CRC mortality by 65-84%[31].	No data from RCTs available yet
Complications	None	Perforation in 1 in 25.000-50.000 FS procedures, the rate of bleeding after polyp removal is <1%.[37]	Perforation rate 1 in 1400 for overall colonoscopies and 1 in 1000 for therapeutic colonoscopies.[38] Mortality 0% in most studies, with the highest reported percentage being 0.02 %.[38]	Perforation risk in screening individuals around 0.005%.[39, 40] Exact cancer risk due to radiation exposure unknown.[41] A single CTC was estimated to increase the life-time cancer risk of a 50-year old by 0.13-0.15% and a 70-year old by 0.07%, although currently lower radiation doses are used.[41, 42] More research on the impact of extracolonic findings is warranted.

* Program sensitivity: sensitivity when an individual participates in subsequent screening rounds, so continuing adherence is of crucial importance for its effectiveness.

[a] *RCT*; Randomized controlled trial

ADVANTAGES OF OFFERING A CHOICE OF SCREENING METHODS

Choice respects individual autonomy

Several studies within the general population have shown that individuals often have a desire for autonomy in medical decisions, although there are differences between subgroups.[33–36] However, these studies usually concerned treatment decisions, which might differ from screening situations. Theoretically, individuals might place more value on autonomy in decisions regarding screening, because they consider themselves healthy and want to ensure that a screening method best corresponds to their preferences. Conversely, people might place less weight on screening decisions, which might seem to have a low impact on personal health for a person who is healthy in principle. In a study on breast cancer screening, 42% of women preferred an active role in decision making, 37% preferred shared decision making, and 20% preferred a doctor-led decision.[37] We did not find any studies that assessed preferences for a single option versus a choice in cancer screening.

Research has consistently shown that individuals have distinct preferences for colorectal screening methods. The characteristics of the screening method have an important role in these preferences.[38–41] Individuals who place a high value on accuracy might choose more invasive methods, whereas those who are deterred by the invasive nature of endoscopic screening might prefer FOBT.[42–44] Likewise, people with limited mobility or resources for travel might have a strong preference for testing at home by FOBT, whereas those who are apprehensive about acquiring or having colorectal cancer might favour examination of the entire colon in a hospital-based setting.

A US study with 168 participants showed that informed decision making changes test preferences in colorectal cancer screening, when offered a choice between FOBT, flexible sigmoidoscopy, colonoscopy, and double-contrast barium enema.[45] Initially, 59% of participants considered FOBT screening their first choice and 28% preferred colonoscopy. Providing individuals with information about benefits and disadvantages of all screening methods resulted in 54% preferring colonoscopy and 26% preferring FOBT.[45] We identified five studies that offered individuals a choice of colorectal cancer screening strategies.[46–50] An Italian study offered participants a choice between FOBT and flexible sigmoidoscopy; of 970 participants, 54% preferred FOBT and 46% chose flexible sigmoidoscopy.[46] In an Australian study, 1333 individuals were offered a choice between FOBT, flexible sigmoidoscopy, colonoscopy, and CT colonography; for 226 (of which 42 participated), the FOBT kit was included in the screening invitation, whereas 220 (of which 50 participated), received the test after contacting the screening organisation by telephone.[47] For those with an FOBT kit included, 66% adhered to FOBT and 27% to colonoscopy, with the rest choosing other strategies. In the group who did not receive an FOBT kit with the initial invitation, 58% adhered to FOBT and 36% to colonoscopy. In a US

study that offered a choice between FOBT and colonoscopy, 55% (n=122) of participants adhered to FOBT and 45% (n=99) to colonoscopy.[48] A Swiss study showed that when 2731 participants were offered a choice between screening methods, 75% underwent colonoscopy, 4% flexible sigmoidoscopy, 10% a combination of flexible sigmoidoscopy and FOBT, and 11% FOBT only.[49] Finally, a US study offered 1672 uninsured participants a choice of colonoscopy, FOBT, or both; 41% participated in colonoscopy screening, 10% in FOBT screening, and 10% in screening with both methods.[50] Additionally, two recent studies among non-participants to flexible sigmoidoscopy screening reported that uptake of FOBT was 19%[51] and 25%,[52] suggesting that for some individuals who prefer screening but for whom flexible sigmoidoscopy is too burdensome, FOBT represents an acceptable screening alternative. A Dutch study found that invitees to colonoscopy screening expected the procedure to be more burdensome than what they experienced, whereas for CT colonography, the procedure was associated with higher burden than what was expected.[53] An Italian study showed that 23% (67 of 287) non-participants to flexible sigmoidoscopy screening mentioned worries about pain, discomfort, or injury as their main reason for non-participation.[54] In conclusion, colorectal cancer screening preferences are distinct and they differ among individuals.

Choice is thought to increase screening participation,[21,42,48,55] possibly due to increased engagement in screening decisions and the capacity for individuals to choose the option that corresponds best with their preferences.[48,55] This is in line with the ideal of patient autonomy, and autonomy is believed to be an important determinant of intrinsic motivation to perform or act on choices made.[56] Furthermore, individuals might not participate if an invasive screening method is offered with no alternative.[42]

Having screening options enhances informed choice

Autonomy requires the ability to make rational, informed choices. Informed choice has been specified as having two core characteristics; it must be based on relevant, good quality information, and the choice must reflect the values of the decision maker.[57] Allowing individuals to choose between screening options enhances informed choice, because it requires knowledge of all possible screening alternatives, including benefits and harms, allowing people to make the choice that corresponds best with their personal values.

Informed choice between screening strategies could be enabled by administering decision aids - ie, interventions that provide information on the relevant screening options and possible health outcomes. Decision aids often contain numerical and graphical risk information, and exercises to facilitate decision making that reflects personal values and preferences. Two studies showed that administering a decision aid for FOBT invitees improved informed decision making (outcomes measured included consistency between attitudes and screening behaviour, decisional conflict, and integration

of knowledge and values),[58,59] although one of the studies noted a significant decrease in participation in the group who received a decision aid versus the group who did not (59% *vs* 75%; p=0.001).[58] A 2009 meta-analysis[60] examined the efficacy of decision aids for helping people faced with difficult decisions about treatment or screening; the study concluded that decision aids performed better than usual-care interventions in improving knowledge, lowering decisional conflict related to feeling uninformed or unclear about personal values, and reducing the proportion of individuals who were passive in decision making or who were undecided.[61] The meta-analysis[60] identified three studies that investigated the effect of decision aids when multiple colorectal cancer screening options were available (FOBT and flexible sigmoidoscopy). Overall, administering a decision aid did not significantly influence screening preferences, and the effect on screening participation differed among studies; one study showed a significant increase in participation among those given a decision aid, whereas another showed a non-significant decrease in participation.[60] A more recent study showed that a decision aid did not significantly increase participation.[61] Currently, evidence on informed decision making in screening with multiple screening options seems inconclusive.

No one screening strategy is superior

No method for screening colorectal cancer has been proven superior when taking all aspects into consideration, including benefits, risks, and costs. There are considerable differences in uptake of colorectal cancer screening in the USA versus Europe, which might be partly influenced by differences in screening policy.[62] In the USA, colonoscopy is often recommended as the primary screening method. In Europe, uptake is usually higher for FOBT screening than for all other screening methods, although endoscopic screening offers higher sensitivity and specificity than FOBT (Table 1). Endoscopic screening also requires less frequent testing, but carries a risk of complications.

Several studies have addressed participant acceptability of colorectal cancer screening methods. A randomised study in Australia compared screenee acceptability of FOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, or a choice of methods.[47] Pain ratings were highest for CT colonography, somewhat lower for flexible sigmoidoscopy, and lowest for colonoscopy. Readiness to attend a successive screening round was high for all methods. The researchers concluded that there was a high level of participant acceptability for all screening methods. Another study, within a Dutch randomised trial of colorectal cancer screening, compared perceived burden and willingness to return for a successive round of gFOBT, FIT, and flexible sigmoidoscopy; 2.5% of FOBT screenees, 1.4% of FIT screenees, and 13% of flexible sigmoidoscopy screenees reported the test or examination to be burdensome.[63] 94% of FOBT screenees, 94% of FIT screenees, and 84% of flexible sigmoidoscopy screenees were willing to attend a successive screening round. Thus, acceptance was high for all screening methods. A recent study compared

participant views on colonoscopy versus CT colonography.[53] Most participants regarded the screening procedures as not or only slightly burdensome, and willingness to attend a next screening round was high: 96% for colonoscopy and 93% for CT colonography. Therefore, based on current data, participant acceptability of all screening methods seems to be high.

From modelling estimations, colonoscopy seems to be the most effective screening strategy for reducing colorectal cancer incidence and mortality, although all screening methods seem to contribute substantially to lowering mortality.[7] Furthermore, on a societal level, all colorectal cancer screening strategies have been shown to be cost-effective.[64] Screening programmes for breast or cervical cancer, even if cost-effective, require substantial net investment. An aspect that distinguishes colorectal cancer screening from other types of cancer screening is that FOBT and flexible sigmoidoscopy are estimated to be cost-saving in the context of the US healthcare system (ie, less expensive than offering no screening) when offering a single screening strategy to the target population, and taking into account rising chemotherapy costs due to newer, more effective treatments.[64] Colonoscopy screening was not shown to be cost-saving, but it is cost-effective. Three European studies concluded that screening with either flexible sigmoidoscopy or colonoscopy was cost-saving.[65–67] It has been calculated that high participation rates are probably not necessary for a cost-effective colorectal cancer screening programme.[68] To our knowledge, only one study has addressed the cost-effectiveness of offering individuals a choice between screening options in a programmatic setting, in the USA.[69] The estimated costs of offering individuals a choice between screening options were based on a weighted average of screening costs that was far below the generally accepted threshold for preventive measures (ie, a cost-effectiveness for choice of US$11 900 per year of life gained, where the generally accepted threshold is $50–100 000).[69] A normative framework for patient choice has been proposed, called evidence-based patient choice.[70–72] Although not specific for screening situations, it aims to enhance patient choice within the boundaries of evidence on effectiveness and costs, including cost-effectiveness.

ADVANTAGES OF OFFERING A SINGLE SCREENING METHOD

Not everyone has an equal desire for autonomy in medical decisions

Several studies among the general population have shown that the desire to be involved in medical decisions differs between individuals.[33–36] For example, studies showed that older age and lower education were associated with less desire for autonomy in medical decisions. Furthermore, choice takes time, and some people might not want to spend their time deliberating about screening options. Some individuals might lack confidence

Table 2 Overview of arguments in favour of a choice of screening methods and of offering a single screening strategy

Advantages of offering a choice between screening strategies	
Choice respects individual autonomy	– Individuals generally have a preference for autonomy in medical treatment decisions – Individuals have distinct preferences regarding CRC screening tests
Choice does justice to the requirement of informed choice	– Informed choice must be based on relevant, good quality information, and the choice must reflect the values of the decision maker. Offering multiple methods enhances informed choice by allowing the preferred the test to reflect the invitees' values.
No specific screening strategy has been shown to be superior	– There is no screening strategy superior to all others taking into account participation, burden, screening frequency, risks, mortality reduction and cost-effectiveness – Screening by both FOBT and FS had been estimated to be even cost-saving compared to no screening.
Advantages of offering a single screening strategy	
Not everyone has an equal desire for autonomy in medical decisions	– Some patients have no desire for autonomy, but prefer to leave the decision with an authority
Choice may lower screening participation	– Choice paradox: one study showed that choice lowered participation; in other studies choice did not increase participation.
Informed decision making on different screening strategies is too complex or laborious	– If the complexity of choice reduces screening rates, for example, mainly among those with lower education, choice reduces equity in the population. – It is more laborious and thereby probably also costly to offer individuals a choice.
Choice is logistically more difficult	– Capacity problems. Choice warrants extra effort to secure quality control and most likely involves more initial organisational costs.
Offering a single test may increase population confidence in health authorities	– Offering a single screening strategy may create reassurance, as individuals may feel insecure if doctors do not know what the best screening option is for them.
Offering a single method places less weight on individual responsibility	– For example, if one chooses FOBT screening and an interval carcinoma is found afterwards, one might experience regret/guilt not having participated in a more sensitive screening strategy (e.g. colonoscopy).

to decide between screening options, or are unsure which option they prefer. Others might simply prefer to follow a clear recommendation for a single screening method.

A 2003 Dutch study investigated autonomous behaviour, ideals of autonomy, and quality of life in patients who had an asymptomatic aortic aneurysm and consulted their surgeon.[72] The group that received an individualised, evidence-based brochure before the consultation had a better understanding of important issues about their treatment decision. However, these preinformed patients were less likely to agree with the surgeon's treatment recommendation, and had less confidence in the doctor's authority. A review by Benbassat and colleagues[73] noted that the only way for physicians to gain insight into a patient's desire to participate in decision making is through direct enquiry; however, this is not feasible in the setting of population-based screening.

Choice might lower screening participation

In three of the studies that offered individuals a choice between colorectal screening methods, having options did not increase participation,[46,48] or even lowered participation rates compared with offering a single strategy.[47] The latter is a surprising finding, referred to as the choice paradox—ie, allowing individuals to choose between screening options actually lowers participation rates instead of increasing them.[74] In a large Italian study with 7381 participants, participation was 30% in the group that received an FOBT every 2 years, 28% in the group invited for flexible sigmoidoscopy screening, and 27% in the group offered a choice between methods.[46] Participation in the choice group did not differ significantly from participation in the whole study population, which was 28.1%. The odds ratio (OR) of participation in the choice group compared with the whole study population was 0.95 (95% CI 0.88–1.04).[46] In an Australian study with 278 participants,[47] participation was 27% for FOBT screening, 16% for CT colonography, and 18% for colonoscopy. Participation was 19% when a choice of screening strategies was offered and an FOBT kit was included in the invitation; participation was 23% when a choice was offered but no FOBT kit was provided. Compared with the group exclusively invited for FOBT screening, participation was significantly lower in the group offered a choice plus FOBT kit (p=0.03), and was non-significantly lower in the group offered a choice without FOBT kit (p=0.3).[47] However, a recent US study (997 participants) reported no decrease in participation when individuals were offered a choice between FOBT and colonoscopy screening versus either strategy alone.[48] Overall adherence was 67% for FOBT alone, 38% for colonoscopy alone, and 70% when a choice between FOBT and colonoscopy was offered. Participation is typically considered a key marker of success for population screening programmes, which aim to lower the burden of disease for the entire population. Therefore, allowing individuals to choose could be ethically problematic if choice lowers participation.

Informed decisions regarding screening might be too complex or laborious

Offering a single method to the target population might facilitate decision making. Invitation letters and information brochures that are focused on a single screening method might improve comprehensibility for the invitee, since less information has to be read and understood. Choice of methods for colorectal cancer screening is particularly difficult since all have advantages and disadvantages, which could result in an invitee doing nothing as a result of confusion. If this complexity reduces screening rates to a greater extent among invitees with lower education than among those with higher education, choice reduces equity in the population.[75] A particular problem that has been shown is that screening uptake is usually lowest among the most socially deprived.[75] An Italian study that offered a choice between colorectal cancer screening tests noted a higher response rate among invitees with a high educational level.[54] A possible strategy to

optimise screening participation has been proposed; those who do not want to make a choice between screening methods could follow the advice of an authoritative health body, while others are given the freedom to make an individual choice.[76] This strategy implies that everyone is offered a choice, but that there is a standard option for those not wanting to choose. This strategy might optimise equity in health care, by preventing lower screening participation among particular groups due to the complexity of choice, and still allow individuals to choose according to their preferences. For those who do not want to make a choice or who are not capable, the screening method with the highest acceptability in the target population could be offered, which might be based on participation in pilot screening programmes. Finally, it might be very laborious and thereby costly to offer individuals a choice between screening options; providing comprehensive information warrants more effort when multiple screening methods are involved (eg, to develop a decision aid).

Choice between screening strategies is logistically more difficult

Allowing individuals to choose between screening strategies will, at least in the beginning, pose a logistic challenge. Facilities for all methods must be available, and extra effort should be taken to ensure screening with all methods is done correctly. Sufficient capacity for colonoscopy is crucial for introduction of a colorectal cancer screening programme, since individuals with a positive FOBT, flexible sigmoidoscopy, or CT colonography are advised to undergo a colonoscopy. The required colonoscopy capacity depends on participation rate, screening method, and the threshold used for defining a positive test. For example, for an equal number of tests, flexible sigmoidoscopy yields a higher number of positive results than FIT, so a higher percentage of participants are referred for colonoscopy. However, participation in FIT screening is often higher than with flexible sigmoidoscopy, so the required colonoscopy capacity might actually be higher for FIT. Not all countries have sufficient endoscopic capacity to give individuals a choice between available screening options. However, endoscopy capacity can be created over time and step-wise implementation can solve this issue (eg, starting with single-test screening, such as FOBT, and offering a choice when sufficient endoscopic capacity is created).

Furthermore, quality assurance is important for all aspects of a screening programme, from patient information and consent to surveillance and treatment of detected disease. Offering a single colorectal cancer screening method to the target population has advantages, since fewer quality control guidelines are needed, and development and adherence to such guidelines might be better. Logistically, the invitation process and registering of participation rates are simpler when one procedure is involved. For example, for FOBT screening, mailing FOBT kits directly to invitees increases screening rates,[77,78] which might not be feasible if individuals first have to decide on their preferred

screening method. Offering a choice of screening methods involves extra effort to ensure quality control, and most likely involves more initial organisational costs.

Offering a single screening method might increase population confidence

Offering a single screening strategy might create reassurance that health authorities and physicians have decided on the best screening strategy on a population level. Individuals might feel insecure if they perceive that doctors or authorities do not know what screening option is best.

Offering a single method places less weight on individual responsibility

Offering a choice between screening strategies places a higher weight on individual responsibility. Recent studies on gFOBT screening every 2 years reported that 23–59% of cancers found in individuals invited for screening were interval cancers, diagnosed between screening rounds after a negative FOBT.[79,80] If an individual chooses to participate in FOBT screening and an interval carcinoma is found afterwards, they might feel regret or guilt at not having chosen a more sensitive screening strategy, such as colonoscopy. By contrast, if a complication arises from colonoscopy screening, a participant might regret not having chosen a less invasive strategy. To our knowledge, no literature has addressed this issue of cancer screening.

DISCUSSION

So far, most population screening programmes (eg, cervical and breast cancer screening) involve a decision on whether or not a single screening method should be introduced. The availability of multiple screening options for colorectal cancer requires a different perspective; a decision must be made on whether or not colorectal cancer screening is introduced, and whether individuals will be offered a single screening strategy (in which case a method must be chosen), or a choice between available options.

The most important arguments in favour of offering a choice between screening methods are that choice enhances autonomy and supports the idea of informed choice, since research has shown that individuals generally have a desire for autonomy in medical decisions and have distinct preferences for colorectal cancer screening strategies. Another argument in favour of a choice of screening strategies is the fact that no specific screening strategy has been shown to be superior when taking all aspects into account. In health care, the principle of clinical equipoise denotes that if there is no evidence that one treatment is better than others, all are offered. In this situation, patient preferences can be an important basis for the decision between options.[81] With current data, it is impossible to determine which colorectal cancer screening method

will be most suitable for a specific population, and individual preferences for screening methods vary.

An argument against autonomy in screening decisions is that not everyone has an equal desire for involvement in medical decisions. Choice might reduce participation, because individuals who would have participated if a single method was offered might not participate if the choice becomes too complex. Some studies have noted lower participation among groups of invitees offered a choice of screening methods compared with groups offered a single option. Lower participation is especially problematic if it occurs to a greater extent in socially deprived groups as a result of confusion. The trade-off between autonomy and loss of health due to non-participation is crucial when considering whether to offer a choice between screening strategies.

There is increasing interest in a two-stage recruitment approach for colorectal cancer screening, whereby a single method is offered first and a different method is offered to non-participants of the first method.[51,52] US guidelines endorse a comparable approach, recommending colonoscopy as a preferred first strategy.[22] The two-stage recruitment approach has important benefits, including removal of the difficulty of choice, simplification of the discussion for physicians, and possible reduced organisational burden for the health system.[51] It has been suggested that this approach might be more effective than offering a choice between screening tests, with regard to participation, overall benefit, and practice efficiency.[51] Furthermore, this approach might reduce inequalities in the population because the element of choice is removed—eg, possibly benefiting those who are less educated. Both education level and factors such as age and sex affect how individuals approach colorectal cancer screening, and how they handle the element of choice. An Italian study reported a higher uptake of flexible sigmoidoscopy among men, whereas the uptake of subsequent FIT was higher among women;[51] this is in accordance with other studies showing a higher uptake of FOBT screening among women and of flexible sigmoidoscopy screening among men.[82]

There are some limitations associated with offering a two-stage strategy within a population-based screening programme. First, enhancement of individual autonomy in health decisions is challenged by this approach. Making an autonomous decision requires adequate alternatives and sufficient information. If individuals are not informed that other alternatives exist when undergoing the first method, an autonomous, informed decision might not have been reached. Second, when invited for a second round of screening, individuals who did not participate in the first option in the previous round will be aware of the two-stage approach, so the benefits of this approach in further screening rounds are to be determined. Furthermore, screenees who refuse a first test might be more inclined to refuse another test, because deciding against the first option became a decision to forgo screening. In line with this observation, a Dutch study showed that overall attendance was higher when flexible sigmoidoscopy

non-participants were subsequently offered FIT (45%) than when only flexible sigmoidoscopy was offered (31%), but lower than when FIT was the only option (62%).[52]

When deciding to offer a single screening strategy, an aspect seldom discussed is whether individuals should be informed that other screening options exist. Informing individuals about the existence of other options supports the requirement of respect for autonomy and informed choice. However, more information might increase confusion, and individuals who would have participated in screening if a single strategy was offered might not be screened, thereby missing out on a possible health gain.

Participation is often regarded as the most important marker of success of a screening programme. Recently, there has been increasing interest in focusing on maximisation of informed choice rather than participation rates, or focusing on consistency between an individual's preference for decision making and their subsequent screening behaviour as a marker for successful screening programmes.[83]

Several factors, for example cost, have an important role in the decision whether or not to offer individuals a choice between screening strategies; however, few studies have addressed this issue. Furthermore, more evidence is needed on the role of choice in uptake of colorectal cancer screening, since current evidence is scarce.[83] So far, literature seems to suggest that choice does not increase, or even reduces, participation.

In conclusion, there are strong arguments in favour of offering individuals a choice between screening strategies, most importantly enhancement of individual autonomy (Table 2). However, this comes at a price; both for the individual (choice is difficult) and on a collective level (logistics are more complicated and costs are higher). The desire for autonomy in screening decisions should be investigated to gain insight into its determinants, as well as the expected societal costs of offering individuals a choice between strategies. To deny individuals a choice of colorectal cancer screening strategies based on the anticipation that choice lowers participation rates, or because multiple options means a more complicated programme introduction, might be oversimplified, and does little justice to individual preferences in an era where several colorectal cancer screening strategies are available and much weight is placed on patient autonomy in healthcare decisions. Arguments in favour and against a choice of colorectal cancer screening strategies should be carefully weighed before introduction of a colorectal cancer screening programme.

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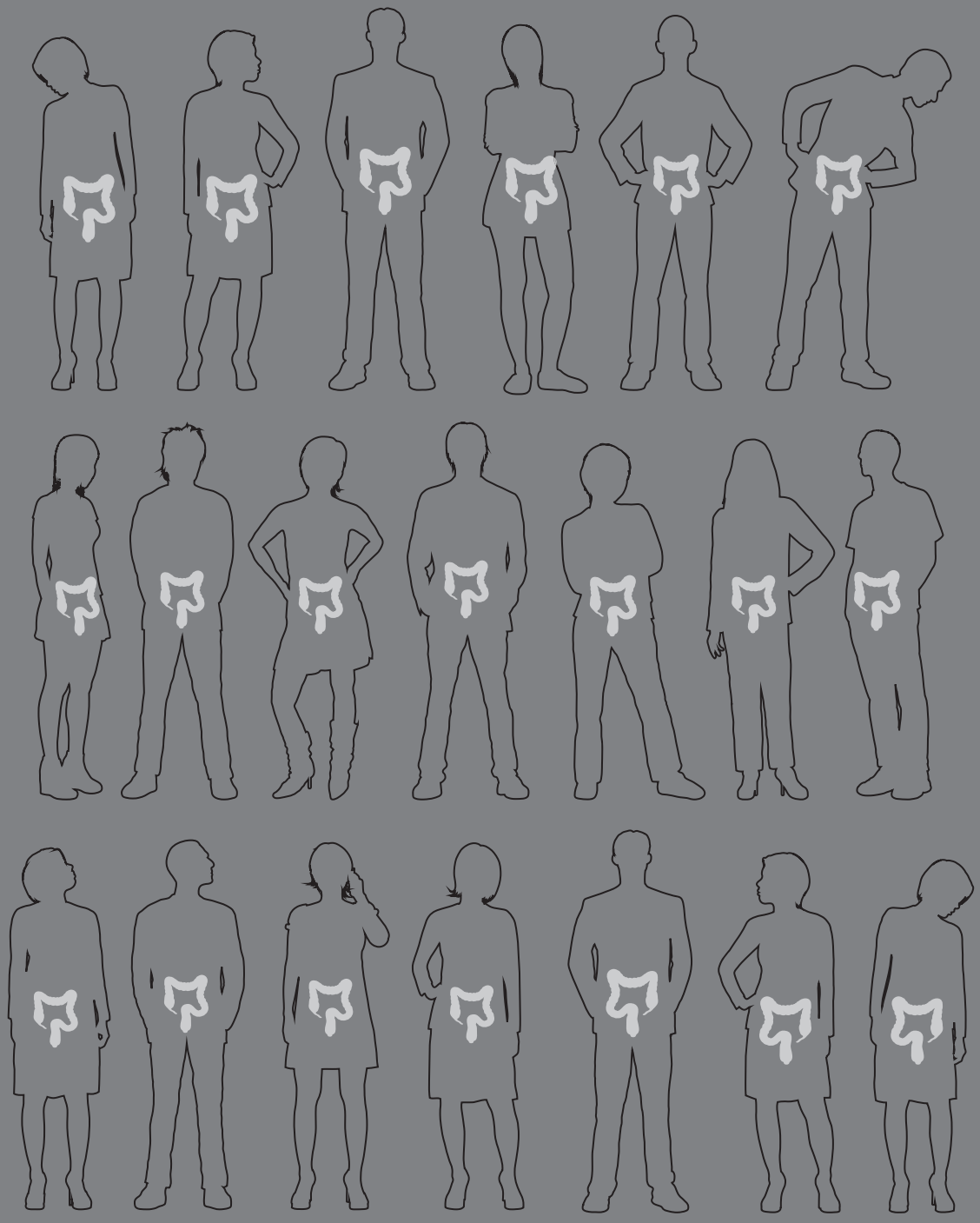
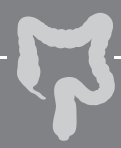


CHAPTER 7

General discussion and conclusion



Colorectal cancer (CRC) screening is a broad, rapidly evolving topic; with large worldwide variation in the chosen approach. The success of population screening for cancer prevention is dependent on many factors. Two explicitly defined factors within the classic Wilson and Jungner screening criteria are the need for a suitable test for examination and the necessity for this test to be acceptable to the target population.[1] One of the criteria that were added in 2008 is the need for a screening programme to ensure informed choice, confidentiality and respect for autonomy.[2] This thesis focuses on those determinants of CRC screening. One of the main factors for successful population screening is the performance of the test used in the screening program; and then in particular the performance of the test within the target population, as the incidence of the disease is different in screening populations compared to patient populations. Secondly, the success of screening is determined by the participation of the target population; which highly depends on the acceptability of the test to that population. This thesis investigates several aspects concerning test performance and determinants of screening participation; and in this line discusses which approach towards colorectal cancer screening will be the optimal.

TEST PERFORMANCE

Faecal occult blood testing (FOBT) is the most commonly adopted screening strategy for population-based screening in Europe.[3] Of the stool based screening tests available, evidence from randomized controlled trials (RCTs) on CRC mortality reduction is available for the guaiac-based FOBT (gFOBT) only[4-8]. Evidence for the fecal immunochemical test (FIT) and fecal DNA testing (sDNA) is limited to data on test performance. However, based on micro-simulation models the effectiveness of FIT-based screening in reducing CRC-related mortality is expected to outperform gFOBT screening.[9] Furthermore, recent trials have indicated that faecal immunochemical testing is superior to the traditionally used gFOBT (i.e., the non-rehydrated Hemoccult II) both with respect to attendance and diagnostic yield of advanced neoplasia.[10-21] There are multiple FIT brands available with many possibilities with regard to the screening strategy (i.e., single or multiple sample FIT screening, in case of quantitative FIT screening, selected cut-off value). This allows for selection of local optimal screening strategies, for instance matching colonoscopy capacity. Due to a limited number of colonoscopy-controlled trials, data on the comparative sensitivity and specificity of different FIT brands are scarce. Since many countries are implementing FIT screening based on current evidence, there will be few countries where RCTs on CRC mortality reduction of the FIT can be carried out as there will be few unscreened control groups available.

Most studies on FIT screening currently published are population-based screening studies in which only those with a positive FIT were referred for further investigations

(i.e. colonoscopy). Therefore, only outcome parameters such as positivity rate (PR), detection rate (DR) and positive predictive value (PPV) are available. These parameters are very relevant for policy makers as they determine for example the required colonoscopy capacity.

In **chapter 2** we therefore performed a systematic review in order to identify the literature available on FIT screening in asymptomatic, average-risk populations regarding PR, DR, and PPV. We included both the qualitative (i.e. requiring a visual interpretation of test results as positive or negative) and quantitative FITs (analysed automatically, providing a value for the amount of haemoglobin found in the stool sample). In total, 50 references met our inclusion criteria. Of these, 25 concerned qualitative FITs; with 14 different brands studied. The other 25 studies concerned quantitative FITs, with 5 different brands studied. There was much variation among the included studies with respect to the PR (3.7 - 35%), the DR of CRC (0.1 – 1.6%), and the DR of advanced adenomas (0.5 – 5.5%). There was no FIT brand superior to all others with regard to the ratio between the PR and the DR of CRC or advanced adenomas. Since different studies used varying numbers of FIT samples per screening round; we also examined the effect of the number of samples performed. When looking at the optimal number of stool samples performed per screening round for all FITs, there seems limited additional value of 2-sample FIT screening compared with 1-sample screening when it comes to the detection of CRC. Only for OC-Sensor Micro, a quantitative FIT brand, 3-sample screening resulted in a significantly higher DR of CRC compared with 1-sample FIT screening. For two other qualitative brands, the RPHA and OC-Hemodia, a third sample did not seem beneficial for the DR of CRC compared with 1-sample screening. For advanced adenomas, a trend was seen towards a higher DR of advanced adenomas when a 2-sample strategy was adopted (for different brand i.e., FOB Gold, Magstream, and OC-Sensor Micro). An explanation for the finding that 2-sample compared with 1-sample FIT screening only increases the DR of advanced adenomas and not of CRC, may be the fact that CRCs are believed to have a more constant bleeding pattern while advanced adenomas are believed to bleed more intermittently. Therefore, it could be hypothesized that when extending the number of performed stool samples especially more advanced adenomas will be detected.

Conclusions and further research

To date, many studies have been published investigating performance characteristics of FIT screening. However, interpretation of this literature is complicated by differences in study design, target populations, definitions of advanced adenomas, first/subsequent screening rounds, and differences in the prevalence of CRC in the target population. Based on the data currently available, there is no FIT superior to others. For an accurate comparison of the performance of the different FITs, studies in which individuals

perform different FITs on the same stool sample are required. Furthermore, improving comparability between studies by applying the uniform criteria and improvement in reporting is warranted.

DETERMINANTS OF CRC SCREENING PARTICIPATION

Screening participation is influenced by many factors; test-related factors such as burden of the test including invasiveness and time required for participation, organizational factors such as preannouncements/reminders, method of invitation, ability to perform the test at home, and subject-related factors such as demographics, barriers (e.g. time-requirements), psychosocial factors including knowledge and awareness of CRC and CRC screening, attitudes towards it, and perceived susceptibility. It is important to identify factors influencing screening participation; as some may be modifiable (e.g. organizational factors, perceived barriers, lack of knowledge) and require action, while others should be respected (well-informed decision on (non-) participation).

Before setting up a population-screening program, it is important to gain insight into the determinants of population preferences for screening strategies. In **chapter 3**, we investigated how procedural characteristics of CRC screening programmes determine preferences for participation and how individuals weigh these against the perceived benefits of participation in CRC screening. This was done by means of a discrete choice experiment (DCE) that was conducted among both screening-naïve subjects and participants of a CRC screening programme. DCE is a survey methodology with its origin in market research, which is increasingly used for health care purposes. 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. All aspects proved to significantly influence the respondents' preferences. On average, respondents required an additional relative risk reduction of CRC-related death by a screening programme of 1% for every additional 10 min of duration of the screening test, 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 l of oral preparation combined with 12 h fasting and 32% to use an extensive bowel preparation. Screening intervals shorter than 10 years were significantly preferred to a 10-year screening interval. The finding that individuals weigh the burden of the test against the perceived mortality reduction is in accordance with previous findings[22-24], while 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. The burden of the required preparation was considered the main drawback

of undergoing CRC screening, which is in line with several other studies.[25-27] 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.[28] Several studies have shown that reassurance may be a motivation for and/or a result of undergoing cancer screening.[29, 30] The preference for shorter screening intervals found in our study may be associated with expected reassurance.

In **chapter 4** we investigated the factors that influenced screening (non-)participation within a randomised screening trial comparing FOBT and flexible sigmoidoscopy (FS) screening. We found that the main reasons for participation in FOBT and FS screening were acquiring certainty about CRC presence (primary reason for 38% and 32% of respondents respectively) and the possibility of early CRC detection (32% and 36% respectively). Anticipated regret and positive attitudes towards CRC screening were strong predictors of actual participation and intention to participate in a next round. The main reason for non-participation in FOBT screening was lack of abdominal complaints (primary reason for 16-24% of the participants (depending on the group)). In previous research, the presence of abdominal complaints was frequently found to be associated with participation in CRC screening.[31-34] Non-participation in FS screening was additionally influenced by worries about burden (main reasons not to participate for 23-38%).

Of all respondents (including non-participants and the screening-naïve group), 77% intended to participate in a next screening round with FOBT and 53% with FS ($p<0.01$). In multivariate analyses, anticipated regret, a neutral or positive attitude towards CRC screening and sufficient knowledge were significant predictors of FOBT screening intention. Male gender, alcohol consumption (compared to no alcohol consumption), having abdominal complaints, knowing someone affected by CRC, a neutral or positive CRC screening attitude, anticipated regret, and a higher perceived personal risk of CRC were positive predictors of FS screening intention.

Eighty-one percent of all participants made an informed choice to participate in CRC screening (sufficient knowledge, positive attitudes and participation). Of all non-participants, 12% made an informed choice in accordance with the criteria (sufficient knowledge, negative attitudes and no participation). Fifty-two percent of non-participants made a choice not in accordance with the criteria for informed choice; choices characterized by sufficient knowledge, positive attitudes towards CRC screening, but no participation. This suggests that for those individuals' barriers such as time-requirements, more important (health) problems or fear played a role in non-participation. While not all those factors may be modifiable, anxiety is a factor that may be influences by information provision. Also, tools such as risk calculators may enhance informed decision making about uptake of screening.[35] In 20% of non-participants knowledge was insuf-

ficient, so this group might benefit from interventions aimed at increasing knowledge. Knowledge of CRC and screening is known to be a positive predictor of CRC screening participation.[32, 36] Our study showed that knowledge of CRC and CRC screening was especially low amongst individuals who had declined both FS and subsequent FOBT.

In **chapter 5** we investigated the time requirements and health effects of participation in CRC screening by colonoscopy and CT-colonography (CTC) within a randomised controlled CRC screening trial. Time requirements may act as barriers for screening participation, however little is known about the actual time-requirements of colonoscopy and CTC screening, even though these are potentially the most time-consuming CRC screening methods. We found that the time to return to routine activities was longer after colonoscopy (3:54 hours, interquartile range (IQR) 1:48–15:00) than after CTC (1:36 hours, IQR 0:54–4:42). The duration of screening-related symptoms after the examination was shorter for colonoscopy (11 hours, IQR 2:54–20) than for CTC (22 hours; IQR 5:30–47; $P < 0.001$). Abdominal complaints were reported more frequently after CTC. Anxiety, pain, and quality of life worsened during the screening process, with no differences between the two examinations. So, compared to colonoscopy, CTC required less time and allowed screenees to return to their daily activities more quickly, but was associated with a twofold longer duration of screening-related symptoms. The latter finding was explained by the use of Telebrix, a non-cathartic iodine-based bowel preparation. A previous study reported that nearly all CTC screenees reported diarrhea after using non-cathartic iodine-based bowel preparation.[37] In our study, also in multivariable analysis, the presence of abdominal complaints on the day after the examination was significantly related to the time it took to feel normal again. Non-cathartic bowel preparation is a relatively new and promising alternative to the currently used cathartic bowel preparations, although it is not currently recommended as there is no evidence from direct comparative studies regarding diagnostic accuracy.[38, 39]

Conclusions and further research

Both **chapter 3 and 4** stress the importance of optimizing information provision to screenees and increasing the understanding of CRC and CRC screening in the population. This thesis shows that individuals have preferences that seem irrational (they prefer shorter to longer screening intervals irrespective of health benefit); and that they also make non-informed choices on CRC screening participation (only 12% of non-participants made an informed choice on screening participation). As there is currently an increasing interest to consider informed choice as a marker of success instead of participation rates[40], optimising information among potential screenees can be considered one of the main targets for improvement of CRC screening programmes. **Chapter 5** aimed to study factors that may contribute to informed decisions making; informing individuals on the actual time requirements of different screening methods (which is mostly relevant

for colonoscopy and CTC screening) may contribute to informed decision making. The time requirements of both colonoscopy and CTC screening are substantial. While the longer duration to return to daily activities after colonoscopy screening compared to CTC screening is important for cost-effectiveness analyses and may possibly be relevant for the job-related consequences for the individual, the quicker return to feeling back to normal may be very relevant form the individual perspective.

For the future more research on (determinants of) informed choice, and in particular how to enhance informed choice, is necessary. It is important to aim for a frequent evaluation of barriers that individuals experience towards CRC screening, to evaluate the success of measures implemented. For CTC screening, both types of preparation for the examination (purgative and limited bowel preparation) should be compared with regard to the duration of abdominal complaints after CTC, as this may be an important aspect in determining the time required to feel completely normal again.

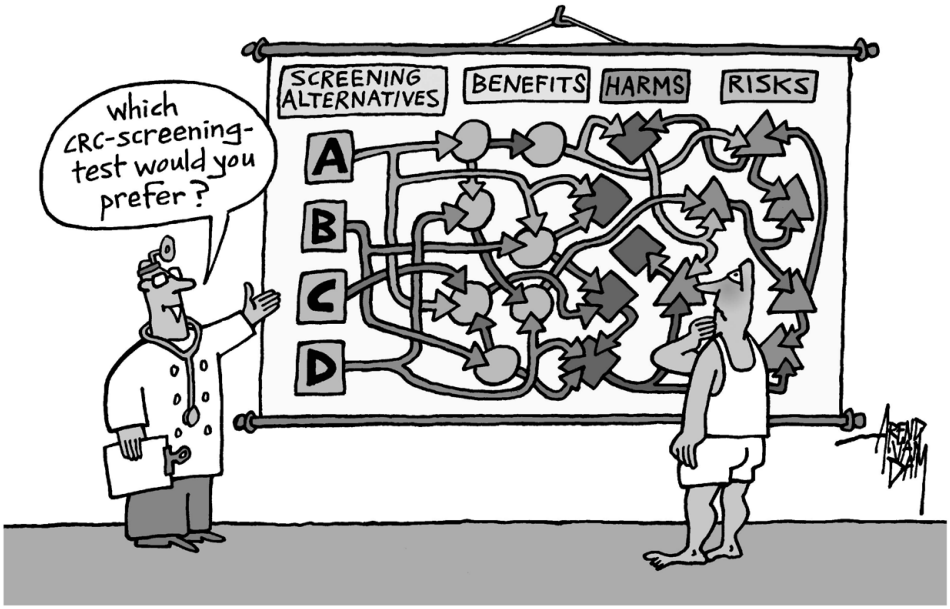
THE OPTIMAL CRC SCREENING PROGRAM

An aspect that discerns CRC screening from other types of cancer screening is the availability of multiple screening methods available for colorectal cancer. These screening methods can be divided into two categories: faecal tests (ie, FOBTs and faecal DNA testing) and structural exams (ie, sigmoidoscopy, colonoscopy, and CT colonography). These methods differ with respect the invasiveness and burden of the procedure, certainty for detecting colorectal cancer (related to the sensitivity and specificity of the method), required screening frequency, and features such as location of screening and handling of stool. In **chapter 6**, we explored the arguments in favour and against giving individuals a choice of CRC screening strategies; based on the evidence currently available.

Worldwide, there is much variation in the preferred screening strategy (i.e., offering individuals a single CRC screening strategy or a choice between available screening strategies). Many experts have advocated offering individuals a choice between available screening methods[41-43], a strategy that has been advocated in the USA.[41] European countries often implement programmatic screening using a single screening strategy.[3]

The most important arguments in favour of offering a choice between screening methods are that choice enhances autonomy and supports the idea of informed choice, since research has shown that individuals generally have a desire for autonomy in medical decisions and have distinct preferences for colorectal cancer screening strategies. Another argument in favour of a choice of screening strategies is the fact that no specific screening strategy has been shown to be superior when taking all aspects into account. In health care, the principle of clinical equipoise denotes that if there is no evidence that one treatment is better than others, all are offered. In this situation, patient preferences

Figure 1 The complexity of choice



can be an important basis for the decision between options.[44] With current data, it is impossible to determine which colorectal cancer screening method will be most suitable for a specific population, and individual preferences for screening methods vary. An argument against autonomy in screening decisions is that not everyone has an equal desire for involvement in medical decisions. Choice might reduce participation, because individuals who would have participated if a single method had been offered might not participate if the choice becomes too complex (Figure 1). Some studies found lower participation among groups of invitees offered a choice of screening methods compared with groups offered a single option. Lower participation is especially problematic if it occurs to a greater extent in socially deprived groups as a result of confusion. The trade-off between autonomy and loss of health due to non-participation is crucial when considering whether to offer a choice between screening strategies.

Conclusions and further research

Our study shows that there are strong arguments in favour of offering individuals a choice between CRC cancer screening strategies. The most important argument is enhancement of individual autonomy, which is an important value in modern Western society. However, choice poses challenges, both for the individual (choice is difficult) and on a collective level (logistics are more complicated and costs are higher). Therefore, more research on the impact of choice on both the individual (participation, informed decision making) and collective (costs of offering a choice) level is warranted. The

desire for autonomy in screening decisions should be investigated to gain insight into its determinants, as well as the expected societal costs of offering individuals a choice between strategies. Furthermore, more research should focus on the effect of choice on screening participation, mainly on the effect on different groups in the population (e.g. those more and less educated). Arguments in favour and against a choice of colorectal cancer screening strategies should be carefully weighed by policy makers in each country prior to the implementation of a colorectal cancer screening programme.

GENERAL CONCLUSIONS

This thesis discusses several aspects of screening for colorectal cancer, from diagnostic accuracy of the fecal immunochemical test, to factors that determine participation in CRC screening, patient experiences with CRC screening, and discussed the advantages and disadvantages of offering individuals a choice between available screening strategies. These results should be used for the improvement of current screening programs, with specific emphasis on the improvement of informed choice in screening. The ethical consideration (chapter 6) should provide guidance for decisions of policy makers on the introduction of a single versus multiple CRC screening strategies.

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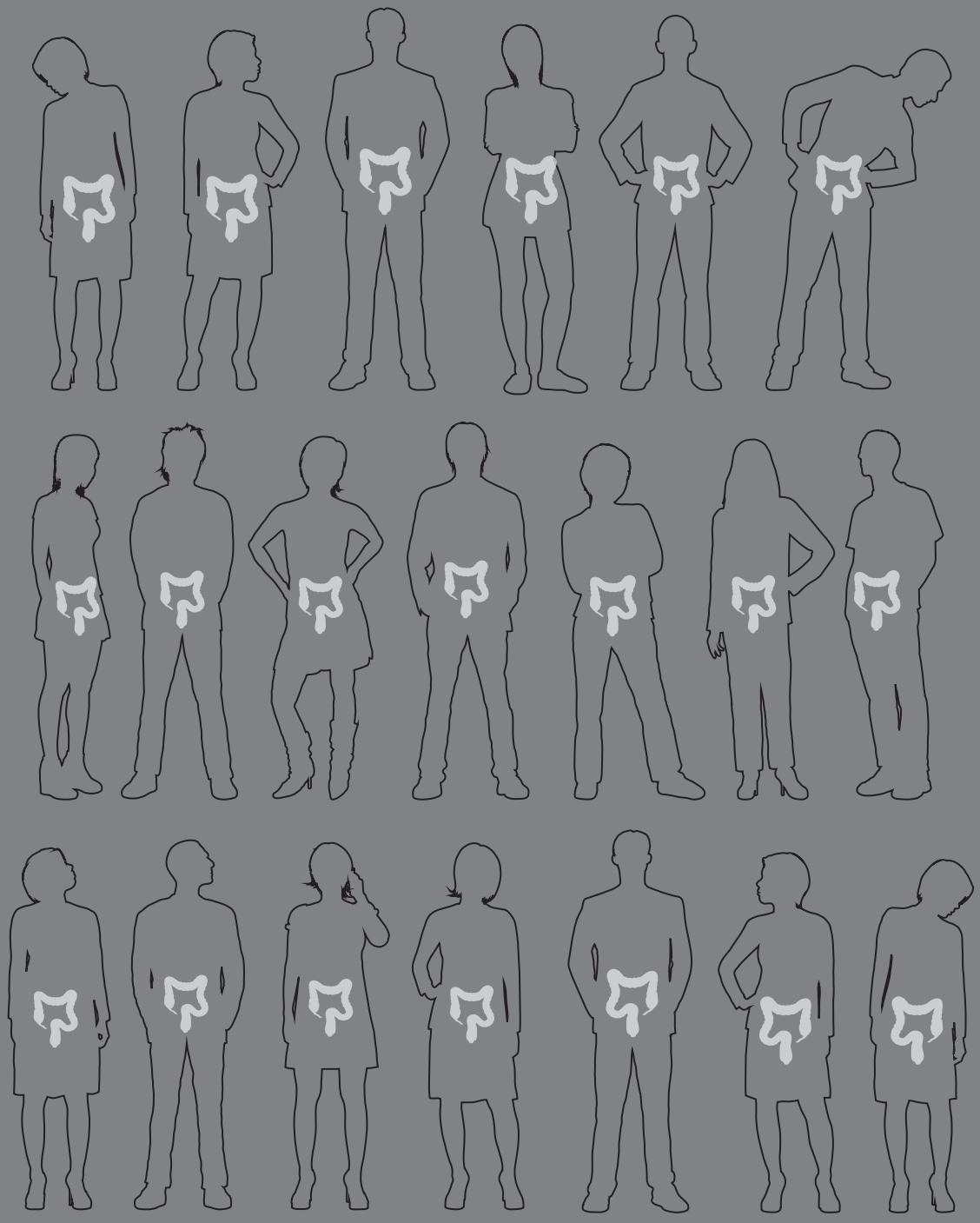


Summary

Chapter 1 provides an introduction on CRC, CRC screening and the available screening methods with their advantages and disadvantages. Furthermore, the aims and outline of the thesis are presented in this chapter. Two explicitly defined factors within the classic Wilson and Jungner screening criteria are the need for a suitable test for examination and the necessity for this test to be acceptable to the target population. One of the criteria that were added in 2008 is the need for a screening programme to ensure informed choice, confidentiality and respect for autonomy.[2] This thesis focuses on those determinants of CRC screening.

For a test to be suitable for population screening, the performance should be adequate. In **chapter 2**, the results of a systematic review on CRC screening with the fecal immunochemical test (FIT) are presented. We aimed to identify the literature available on FIT screening in asymptomatic, average-risk populations regarding PR, DR, and PPV, as these performance characteristics are most widely studied and determinants of the required colonoscopy capacity. In total, 50 articles were identified. We found that there is no FIT brand superior to all others with respect to these performance characteristics. Furthermore, interpretation of the literature currently available is complicated by differences in study design, target populations, definitions of advanced adenomas, first/subsequent screening rounds, and differences in the prevalence of CRC in the target population. Therefore, it is currently impossible to draw conclusions on the best available FIT. For an accurate comparison of the performance of the different FITs, studies in which individuals perform different FITs on the same stool sample are required. Furthermore, improving comparability between studies by applying the uniform criteria and improvement in reporting is warranted.

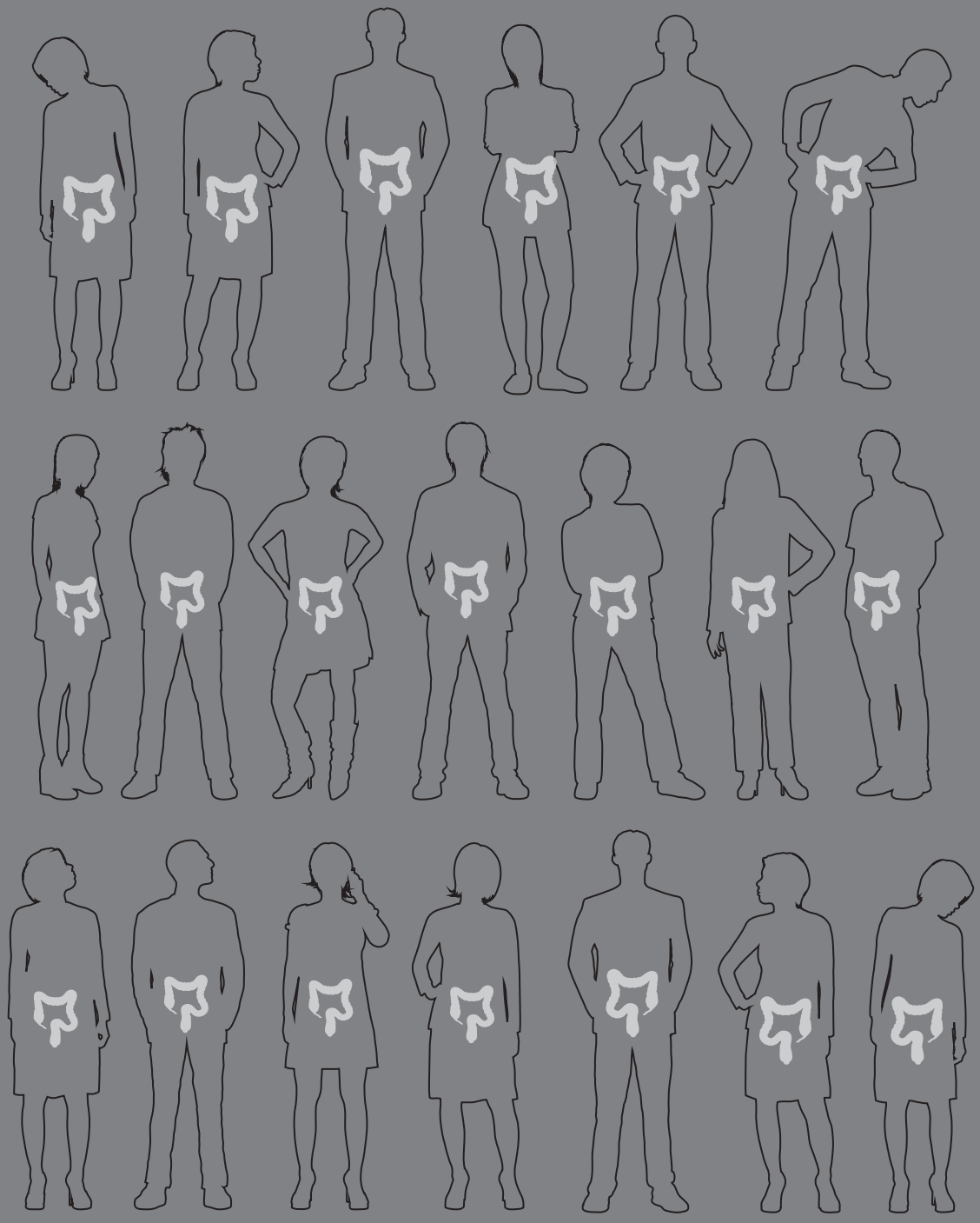
Before setting up a population-screening program, it is important to gain insight into the determinants of population preferences for screening strategies. In **chapter 3**, we investigated how procedural characteristics of CRC screening programmes determine preferences for participation and how individuals weigh these against the perceived benefits of participation in CRC screening. This was done by means of a discrete choice experiment (DCE) that was conducted among both screening-naïve subjects and participants of a CRC screening programme; aged 50-74. DCEs measure preferences for health care interventions, assuming that preferences for a test are determined by the test characteristics. The screening test options are is presented as 'A', 'B', or 'C; and the tests are further described by their test characteristics. We found that especially type of bowel preparation, risk reduction of CRC related death and length of screening interval influence CRC screening preferences. Furthermore, given the fact that individuals preferred shorter screening intervals to a 10-year screening interval irrespective of health benefit suggests that improving awareness on CRC mortality reduction by CRC screening may increase uptake.

In **chapter 4** we investigated the factors that influenced screening (non-)participation within a randomized screening trial comparing FOBT and flexible sigmoidoscopy (FS) screening, aged 50-74. Furthermore, we invited a reference group from the same population not previously invited (screening naïve group). We found that the main reasons for FOBT and FS participation were acquiring certainty about CRC presence and the possibility of early CRC detection. Anticipated regret and positive attitudes towards CRC screening were strong predictors of actual participation and intention to participate in a next round. The main reason for non-participation in FOBT screening was lack of abdominal complaints. Non-participation in FS screening was additionally influenced by worries about burden. Eighty-one percent of participants and 12% of non-participants made an informed choice on participation. The results of this study imply that governments and/or health care organizations offering screening should focus on adequately informing and educating target populations about harms and benefits of CRC screening. This may impact uptake of CRC screening.

In **chapter 5** we investigated the time requirements and health effects of participation in CRC screening by colonoscopy and CTC within a randomized controlled CRC screening trial. Time requirements may act as barriers for screening participation, however little is known about the actual time-requirements of colonoscopy and CTC screening, even though these are potentially the most time-consuming CRC screening methods. We found that compared to colonoscopy, CTC required less time and allowed screenees to return to their daily activities more quickly (CTC 1:36 hours, interquartile range (IQR) 0:54-4:42; colonoscopy 3:54 hours, IQR 1:48-15:00), but was associated with a twofold longer duration of screening-related symptoms (CTC 22 hours, IQR 5:30–47; colonoscopy 11 hours, IQR 2:54–20; $P < 0.001$). Abdominal complaints were reported more frequently after CTC. Anxiety, pain, and quality of life worsened during the screening process, with no differences between the two examinations. From a cost-effectiveness perspective, mainly the time required before returning to routine activities may be relevant, while from an individuals' perspective mainly the time to return to feeling back to normal may be relevant.

An aspect that discerns CRC screening from other types of cancer screening is the availability of multiple screening methods available for colorectal cancer. These methods differ with respect to the invasiveness and burden of the procedure, certainty for detecting colorectal cancer (related to the sensitivity and specificity of the method), required screening frequency, and features such as location of screening and handling of stool. Worldwide, there is much variation in the preferred screening strategy (i.e., offering individuals a single CRC screening strategy or a choice between available screening strategies). In **chapter 6**, we explored the arguments in favour and against giving individuals a choice of CRC screening strategies; based on the evidence currently available. The most important arguments in favour of offering a choice between screening methods are that

choice enhances autonomy and supports the idea of informed choice, since research has shown that individuals generally have a desire for autonomy in medical decisions and have distinct preferences for colorectal cancer screening strategies. An important argument against autonomy in screening decisions is that not everyone has an equal desire for involvement in medical decisions, and research has shown that choice might reduce participation. Arguments in favour and against a choice of colorectal cancer screening strategies should be carefully weighed in each country introducing CRC screening before introducing a colorectal cancer screening programme.



Nederlandse samenvatting

Hoofdstuk 1 geeft een introductie over dikke darmkanker, het bevolkingsonderzoek naar dikke darmkanker en de onderzoeksmethoden die beschikbaar zijn voor het bevolkingsonderzoek met hun voor- en nadelen. In dit hoofdstuk wordt ook een overzicht gegeven van de doelen en inhoud van het proefschrift. In de algemeen gerespecteerde criteria voor verantwoord bevolkingsonderzoek, opgesteld door Wilson en Jungner, staat dat er een geschikte test moet zijn voor het bevolkingsonderzoek en dat die test acceptabel moet zijn voor de bevolking. Eén van de criteria die in een update in 2008 werd toegevoegd is dat er bij invoering van een bevolkingsonderzoek moet worden gezorgd dat geïnformeerde keuze, vertrouwelijkheid en respect voor autonomie gewaarborgd zijn. Dit proefschrift richt zich op deze determinanten van bevolkingsonderzoek naar dikke darmkanker.

Een test moet goed genoeg presteren om geschikt te zijn voor een bevolkingsonderzoek. In **hoofdstuk 2** hebben we middels een systematisch review gekeken naar de testprestaties van de immunochemische feces occult bloed test (FIT). Het doel van dit onderzoek was alle literatuur die beschikbaar is over de testprestaties van de FIT te identificeren. Daarbij is gekeken naar het positiviteitspercentage, de detectiegraad en positief voorspellende waarde, omdat dit de testkarakteristieken zijn die het meest onderzocht zijn en die tevens bepalend zijn voor de benodigde colonoscopie capaciteit. In totaal voldeden 50 artikelen aan de inclusie criteria. Het review liet zien dat er op basis van de huidige data niet één FIT beter is dan anderen op basis van deze testkarakteristieken. De literatuur bleek lastig te vergelijken te zijn als gevolg van verschillen in studie opzet, deelnemers, definitie van advanced adenomen, eerste screeningsronde/vervolgronden, en verschillen in de prevalentie van dikke darmkanker in de studie populatie. Op het moment is het niet mogelijk conclusies te trekken over de beste FIT. Voor een goede vergelijking moeten er studies worden uitgevoerd waarin deelnemers verschillende FITs op één ontlastingmonster toepassen. Ook moeten studies dezelfde criteria en methoden van rapportage gaan toepassen om de vergelijkbaarheid tussen studies te vergroten.

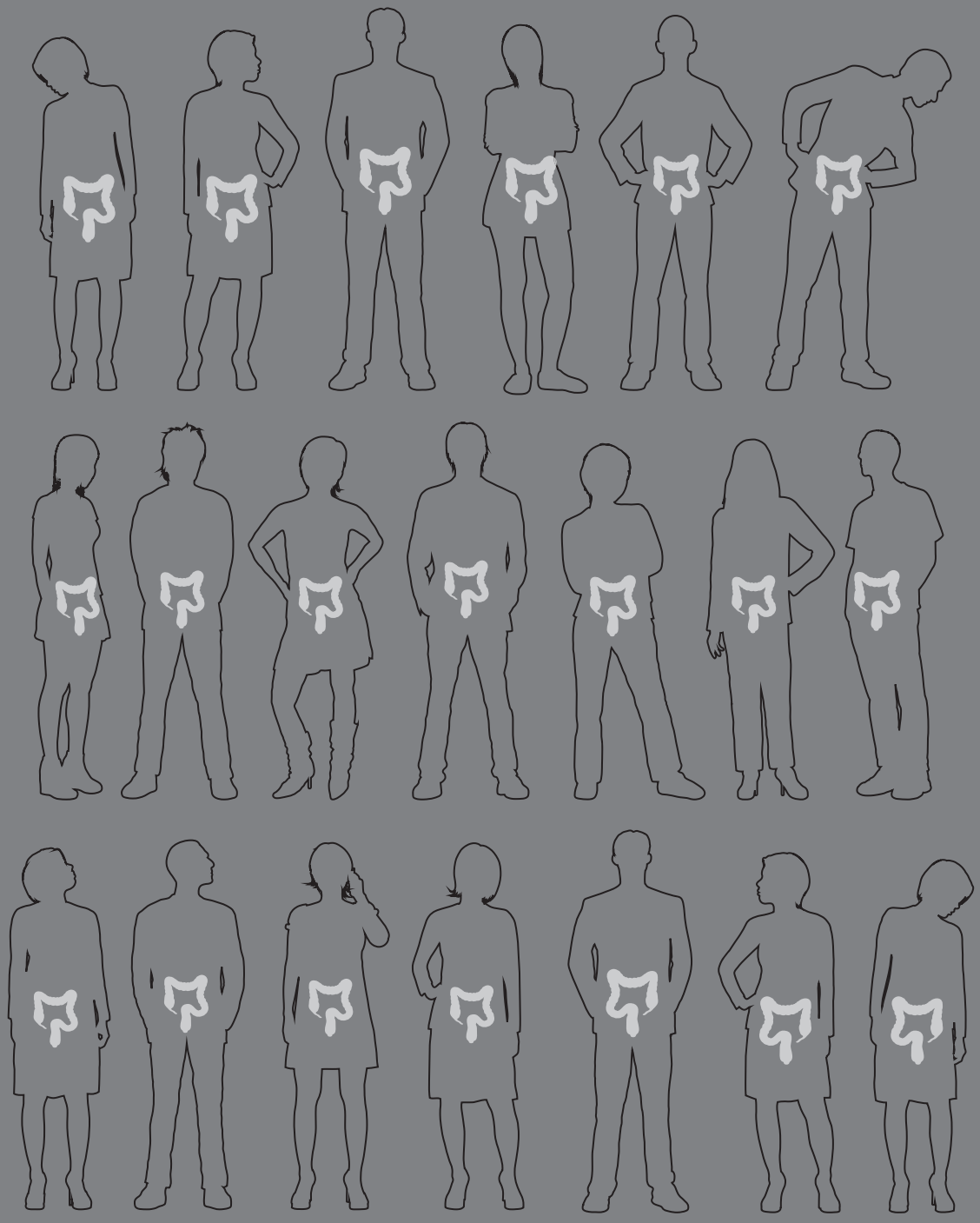
Voordat een bevolkingsonderzoek kan worden opgezet is het belangrijk om inzicht te verkrijgen in de voorkeuren in de populatie aangaande dat bevolkingsonderzoek. In **hoofdstuk 3** hebben we onderzocht hoe bepaalde karakteristieken van de verschillende onderzoeksmethoden die beschikbaar zijn voor het bevolkingsonderzoek naar darmkanker de bereidheid tot deelname beïnvloeden. Tevens werd gekeken hoe mensen de voordelen die het bevolkingsonderzoek met zich meebrengt afwegen tegen de nadelen. Dit werd onderzocht middels een diskreet keuze experiment (DKE), welke werd uitgevoerd onder zowel mensen met, als mensen zonder ervaring met het bevolkingsonderzoek naar darmkanker in de leeftijdsklasse 50-74 jaar. DKEs meten de preferenties voor interventies in de gezondheidszorg, en gaan ervan uit dat preferenties voor een onderzoeksmethode worden bepaald door de karakteristieken van dat onderzoek (bijvoorbeeld de locatie, wel/geen voorbereiding). De verschillende opties worden ge-

presenteerd als "A","B", of "C"; en de onderzoeken worden verder beschreven aan de hand van de karakteristieken. We vonden dat met name de manier van darmvoorbereiding, risicoreductie van overlijden aan darmkanker en het screeningsinterval (bijvoorbeeld 1, 2 of 3 jaar) van invloed waren op de voorkeuren betreffende het bevolkingsonderzoek naar darmkanker. Het feit dat mensen kortere screeningsintervallen prefereerden boven een 10-jaars interval wekt de suggestie dat het belangrijk is om te zorgen dat de kennis over het bevolkingsonderzoek naar dikke darmkanker wordt vergroot.

In **hoofdstuk 4** hebben we onderzocht welke factoren van invloed waren op (niet-) deelname aan feces occult bloed (FOBT; een ontlastingstest) en sigmoïdoscopie screening. Dit werd vergeleken met mensen die nog nooit waren uitgenodigd voor het bevolkingsonderzoek naar damkanker. De belangrijkste redenen om deel te nemen aan het bevolkingsonderzoek naar darmkanker waren het verkrijgen van zekerheid over de aanwezigheid van darmkanker en de mogelijkheid tot vroege opsporing van darmkanker. Geanticipeerde spijt en een positieve houding ten opzichte van het bevolkingsonderzoek naar dikke darmkanker waren sterke voorspellers van deelname en de intentie in een volgende screeningsronde opnieuw deel te nemen. De belangrijkste reden om niet deel te nemen was de afwezigheid van darmklachten. Niet-deelname werd tevens beïnvloed door zorgen over de belasting van de test. Van de deelnemers maakte 81% een geïnformeerde keuze over deelname, van de niet-deelnemers maakte 12% een geïnformeerde keuze over niet-deelname. De resultaten van deze studie benadrukken het belang van adequate informatievoorziening omtrent de voor- en nadelen van het bevolkingsonderzoek naar darmkanker door organisaties in de gezondheidszorg en de regering. Dit kan de deelname aan het bevolkingsonderzoek naar dikke darmkanker beïnvloeden.

In **hoofdstuk 5** keken we naar de tijd die deelnemers kwijt waren aan colonoscopie en CT-colografie (CTC), binnen een gerandomiseerd proefbevolkingsonderzoek. De tijdsinvestering bij deze twee onderzoeksmethoden lijkt aanzienlijk en kan een belemmering tot deelname zijn, echter er is weinig bekend over de tijd die deelname aan deze onderzoeken daadwerkelijk kost. Wij vonden dat, in vergelijking met colonoscopie, CTC deelnemers sneller hun dagelijkse activiteiten konden hervatten (CTC 1:36 uur, interkwartielafstand (IKA) 0:54-4:42; colonoscopie 3:54 uur, IKA 1:48-15:00). CTC ging echter gepaard met een tweemaal langere duur van screenings-gerelateerde klachten (CTC 22 uur, IKA 5:30–47; colonoscopie 11 uur, IKA 2:54–20; $P < 0.001$). Darmklachten werden vaker gerapporteerd na CTC screening dan na colonoscopie screening. Angst, pijn en kwaliteit van leven verslechterden tijdens het screeningsproces, zonder verschil tussen CTC en colonoscopie. Vanuit een kosten-effectiviteitspersepctief, zou met name de tijdsduur tot het hervatten van de dagelijkse bezigheden relevant kunnen zijn, terwijl vanuit het perspectief van het individu met name de duur van screenings-gerelateerde klachten van belang kan zijn. De verschillen in tijdsinvestering zouden in toekomstige kosten-effectiviteitsanalyses moeten worden meegenomen.

Een aspect dat het bevolkingsonderzoek naar dikke darmkanker onderscheidt van andere soorten bevolkingsonderzoek is dat er verschillende onderzoeksmethoden beschikbaar zijn. Deze methoden verschillen met betrekking tot de belasting van het onderzoek, de zekerheid die het geeft over aan- of afwezigheid van darmkanker, de benodigde frequentie, en eigenschappen zoals de locatie waar het onderzoek plaats vindt. Wereldwijd is er veel variatie in de strategie die wordt verkozen; sommige landen bieden deelnemers een enkele test aan; andere landen geven de keuze tussen verschillende testen. In **hoofdstuk 6** wordt gekeken naar de argumenten voor en tegen het geven van een keuze tussen onderzoeksmethoden, op basis van de literatuur die beschikbaar is. Het belangrijkste argument voor een keuze tussen onderzoeksmethoden is dat het de autonomie vergroot en zorgt voor een geïnformeerde keuze; aangezien onderzoeken laten zien dat individuen over het algemeen genomen een voorkeur hebben voor autonomie in medische beslissingen, tevens hebben ze uiteenlopende voorkeurende aangaande de onderzoeken die beschikbaar zijn voor het bevolkingsonderzoek. Belangrijke argumenten tegen een keuze zijn dat niet iedereen een wens heeft om betrokken te zijn in medische beslissingen en onderzoek heeft laten zien dat keuzevrijheid mogelijk de deelname verlaagt. Argumenten voor en tegen een keuze uit onderzoeksmethoden voor het bevolkingsonderzoek naar dikke darmkanker moeten zorgvuldig worden afgewogen voordat dit bevolkingsonderzoek wordt ingevoerd.



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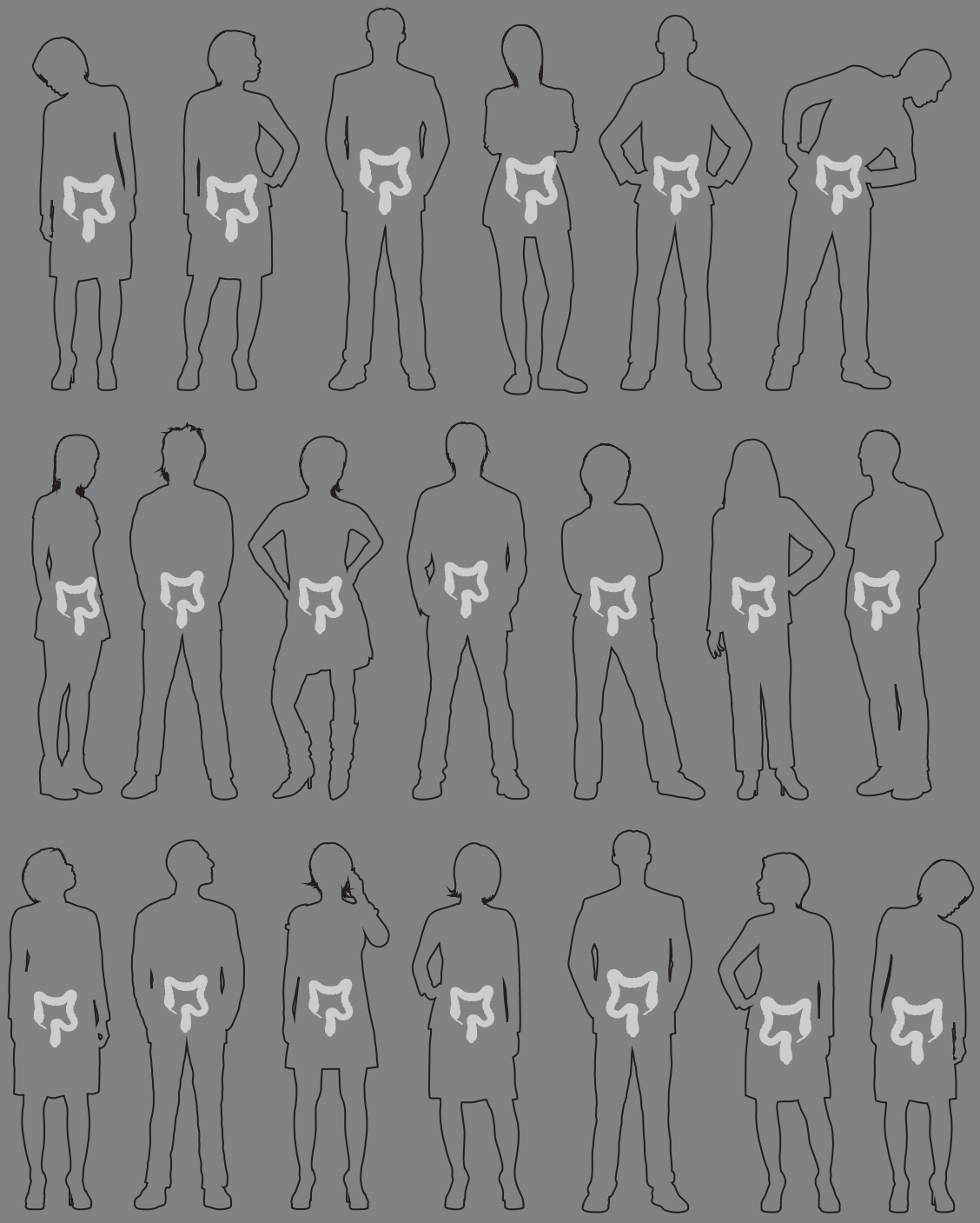
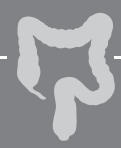
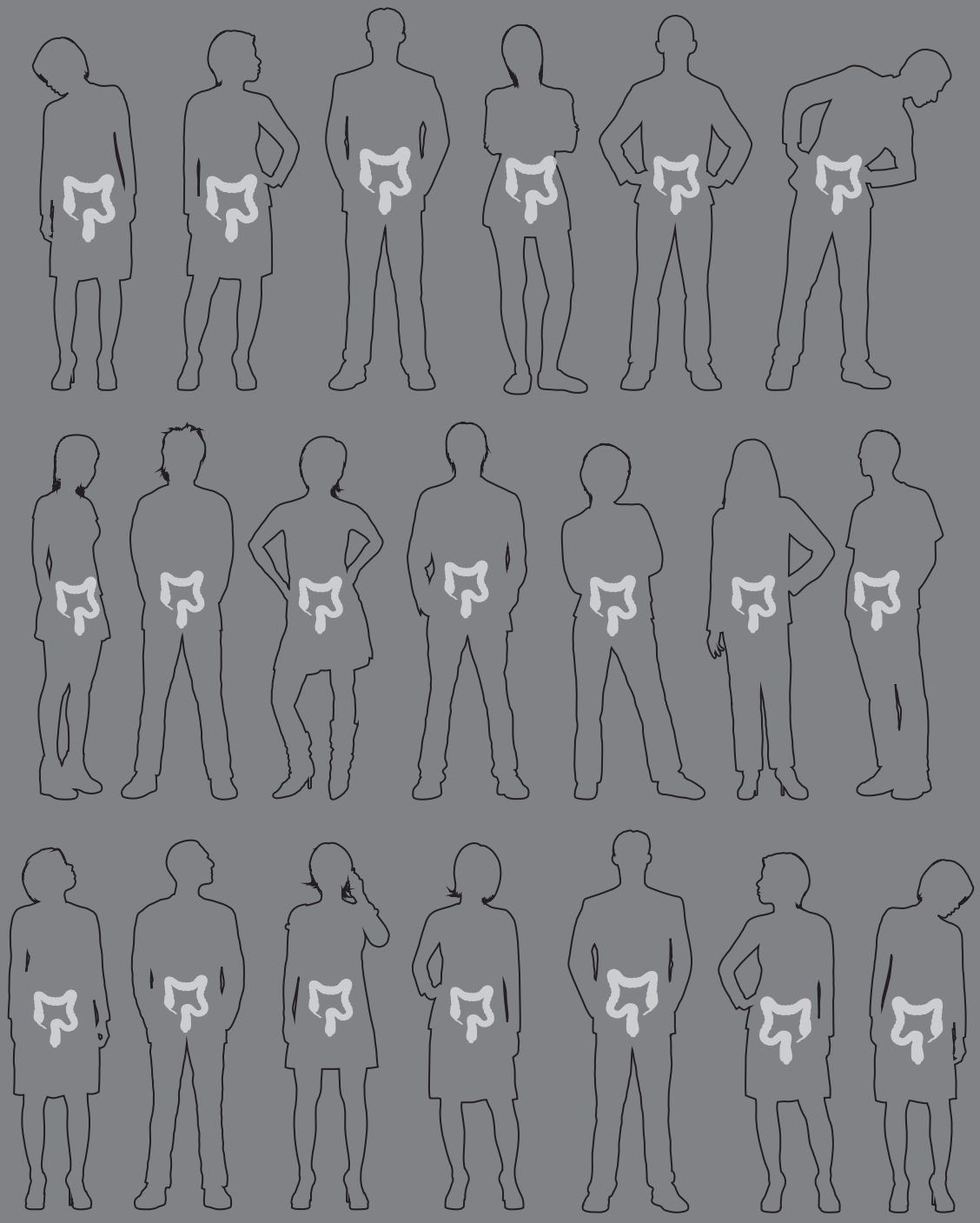


Curriculum Vitae

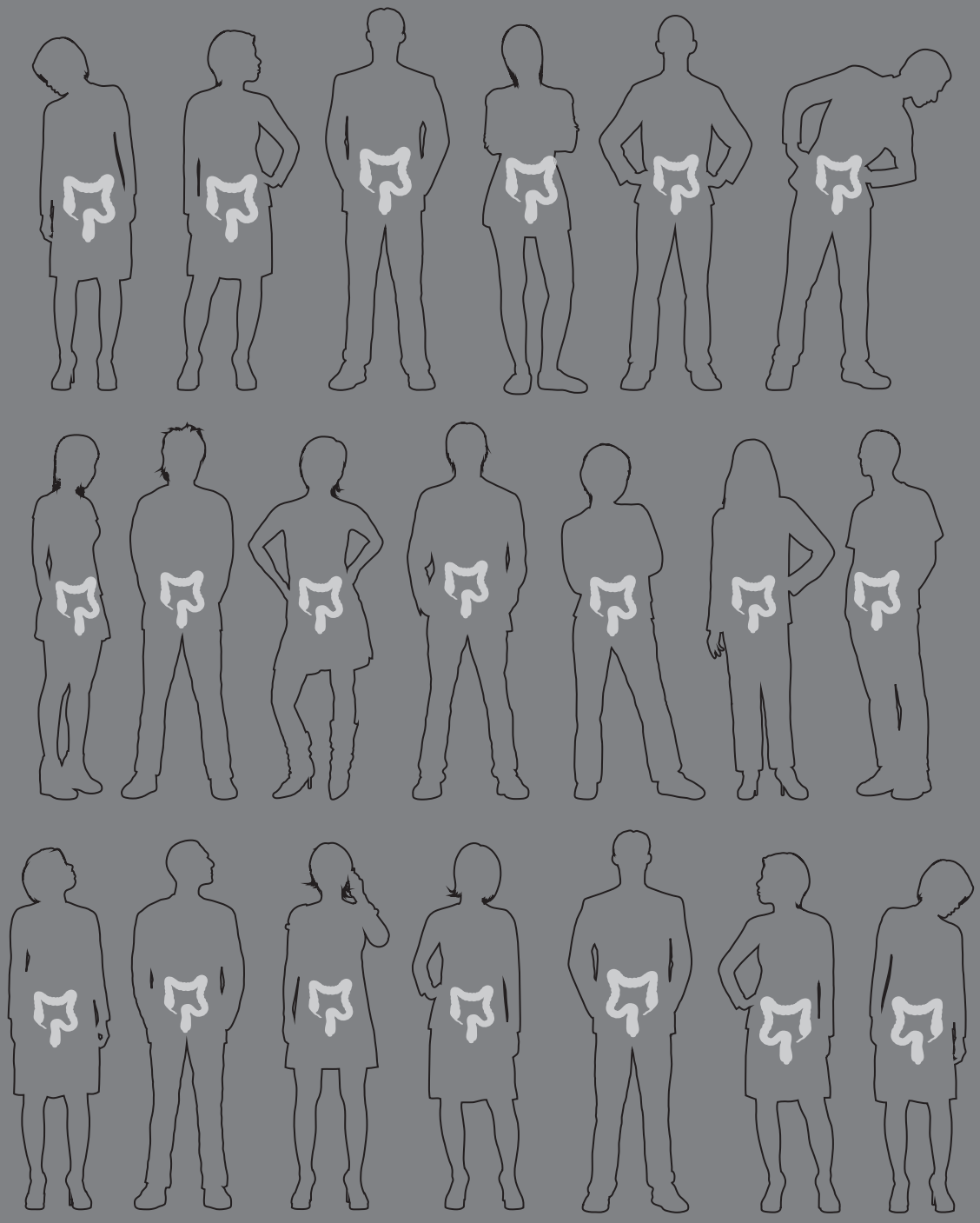


Leonie van Dam werd geboren op 11 januari 1985 te Voorburg. In 2002 behaalde zij haar eindexamen aan het Gymnasium Sorghvliet te 's-Gravenhage. Na een jaar in Groningen te hebben gestudeerd startte zij in 2003 met de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. Tijdens haar studie was zij werkzaam als student-assistent op de afdeling Medische Ethiek, waarbij zij participeerde in diverse internationale congressen. Haar afstudeeronderzoek deed zij op de afdelingen Maag-, Darm- en Leverziekten en Medische Ethiek, en daaruit kwam haar promotieonderzoek voort. Voordat zij startte met haar co-schappen deed zij van oktober 2008 tot februari 2011 promotieonderzoek betreffende het bevolkingsonderzoek naar colorectaal carcinoom, onder leiding van haar promotoren professor E.J. Kuipers (Maag-, Darm- en Leverziekten), professor I.D. de Beaufort (Medische Ethiek) en professor E.W. Steyerberg (Maatschappelijke Gezondheidszorg), en haar co-promotor dr. M.E. van Leerdam. Nadat zij haar co-schappen afrondde is zij in april 2013 gestart met de opleiding tot Maag-, Darm- en Leverarts vanuit het Erasmus MC (opleider dr. R.A. de Man). De eerste vier jaar van haar opleiding volgt zij in het Albert Schweitzer Ziekenhuis te Dordrecht met als opleiders dr. E.F.H. van Bommel (Interne Geneeskunde) en dr. R. Beukers (Maag-, Darm- en Leverziekten).

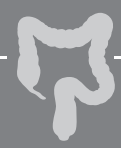


List of publications

1. van Dam L, Hol L, de Bekker-Grob EW, Steyerberg EW, Kuipers EJ, Habbema JDF, Essink-Bot ML, van Leerdam ME. What determines individuals' preferences for colorectal cancer screening programmes? A discrete choice experiment. Eur J Cancer, 2010;46(1):150-159.
2. van Dam L, Kuipers EJ, van Leerdam ME. Performance improvements of stool-based screening tests. Best Pract Res Clin Gastroenterol, 2010;24(4):479-492.
3. van Dam L, van Roon AHC, Zauber AG, van Ballegooijen M, Borsboom GJJM, Steyerberg EW, van Leerdam ME, Kuipers EJ. Guaiac-based faecal occult blood tests versus faecal immunochemical tests for colorectal cancer screening in average-risk individuals (Protocol). Cochrane Database of Systematic Reviews 2011, Issue 8. Art. No.: CD009276. DOI: 10.1002/14651858.CD009276.
4. van Dam L, de Wijkerslooth TR, de Haan MC, Stoop EM, Bossuyt PMM, Fockens P, Thomeer M, Kuipers EJ, van Leerdam ME, van Ballegooijen M, Stoker J, Dekker E, Steyerberg EW. Time requirements and health effects of participation in colorectal cancer screening with colonoscopy or computed tomography colonography in a randomized controlled trial. Endoscopy 2013;45(3):182-8.
5. van Dam L, van Roon AHC, Arends LR, Zauber AG, Young GP, van Ballegooijen M, van Leerdam ME, Steyerberg EW, Kuipers EJ. Faecal immunochemical tests for colorectal cancer screening in average-risk individuals. Submitted.
6. van Dam L, Korfage I, Kuipers EJ, Hol L, van Roon AHC, Reijerink JCIY, van Ballegooijen M, van Leerdam ME. What influences the decision to participate in colorectal cancer screening with faecal occult blood testing and sigmoidoscopy? Eur J Cancer 2013;49(10):2321-2330.
7. van Dam L, Kuipers EJ, Steyerberg EW, van Leerdam ME, de Beaufort ID. The price of autonomy: should we offer individuals a choice between colorectal cancer screening strategies? Lancet Oncol 2013;14(1):e38-e46.
8. van Dam L. Bevolkingsonderzoek naar darmkanker. In: de Beaufort ID, Hilhorst MT, Vandamme S, van de Vathorst S. De Kwestie; Praktijkboek ethiek voor de gezondheidszorg. Lemma, ISBN: 9789059310681; Hoofdstuk 26.
9. Hol L, de Bekker-Grob EW, van Dam L, Donkers B, Kuipers EJ, Habbema JDF, Steyerberg EW, van Leerdam ME, Essink-Bot ML. Preferences for colorectal cancer screening strategies: a discrete choice experiment. Br J Cancer 2010;102(6);972-980.
10. de Bekker-Grob EW, Hol L, Donkers B, van Dam L, Habbema JDF, van Leerdam ME, Kuipers EJ, Essink-Bot ML, Steyerberg EW. Labeled versus unlabeled discrete choice experiments in health economics: an application to colorectal cancer screening. Value Health 2010;13(2):315-23.



PhD portfolio



ORAL PRESENTATIONS

2011
Perceived burden and time investment of colorectal cancer screening by colonoscopy or CT-colonography: a randomized controlled trial
Dutch Society of Gastroenterology, Veldhoven, the Netherlands

2010
Results of discrete choice experiments on colorectal cancer screening
Dutch Cancer Society

2008
Population preferences for different screening strategies for colorectal cancer in the Netherlands; a discrete choice experiment
United European Gastroenterology Week, Vienna, Austria

POSTER PRESENTATION

2012
The price of autonomy: Should individuals be offered a choice between colorectal cancer screening strategies?
World Congress of Bioethics, Rotterdam, the Netherlands

2011
Individuals' time invested in participating in colorectal cancer screening with colonoscopy or CT-colonography
Digestive Disease Week, Chicago, United States

2010
Comparing participants and non-participants of a randomized colorectal cancer screening program using guaiac-based and immunochemical fecal occult blood test and flexible sigmoidoscopy
Digestive Disease week, New Orleans, United States

Comparison of participants and non-participants in a flexible sigmoidoscopy program, with an alternative invitation for fecal immunochemical testing
Digestive Disease week, New Orleans, United States

Experiences of general practitioners regarding their role in the referral process for colonoscopy after a positive colorectal cancer screening test
Digestive Disease week, New Orleans, United States

2009
What determines individuals' preferences for colorectal cancer screening tests?
Digestive Disease week, New Orleans, United States

ATTENDED SEMINARS AND WORKSHOPS

2010
Cochrane Systematic Reviews of Diagnostic Test Accuracy
Academic Medical Centre, Amsterdam, the Netherlands

Developing a Cochrane Systematic Review
Academic Medical Centre, Amsterdam, the Netherlands

2009
Discrete choice experiments in health care
Department of Public Health, Erasmus University Medical Centre, Rotterdam, the Netherlands

Erasmus Summer Program: Biostatistics for Clinicians
Erasmus University Medical Centre, Rotterdam, the Netherlands

MS Access database, Basis course
Erasmus University Medical Centre, Rotterdam, the Netherlands

PEER REVIEW ACTIVITIES

European Journal of Cancer