Health Effects and Costs of Colorectal Cancer Screening

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This one goes out to the ones I love

(R.E.M.)

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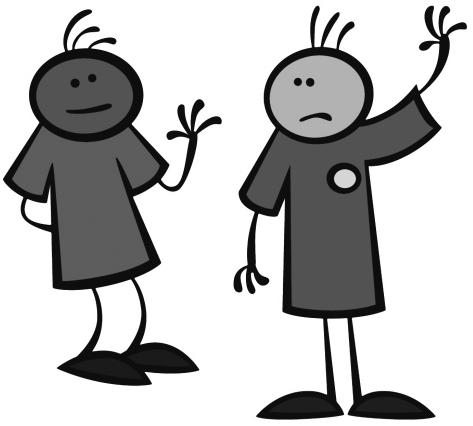
Introduction



EPIDEMIOLOGY

Colorectal cancer (CRC) is a major public health problem, with over a million newly diagnosed cases per year worldwide.[1] CRC occurs especially frequently in established market economies like Europe, the United States (US), Canada, Australia and Japan (Figure 1-1). The lifetime incidence in average risk individuals in these regions is approximately 5%.[2]

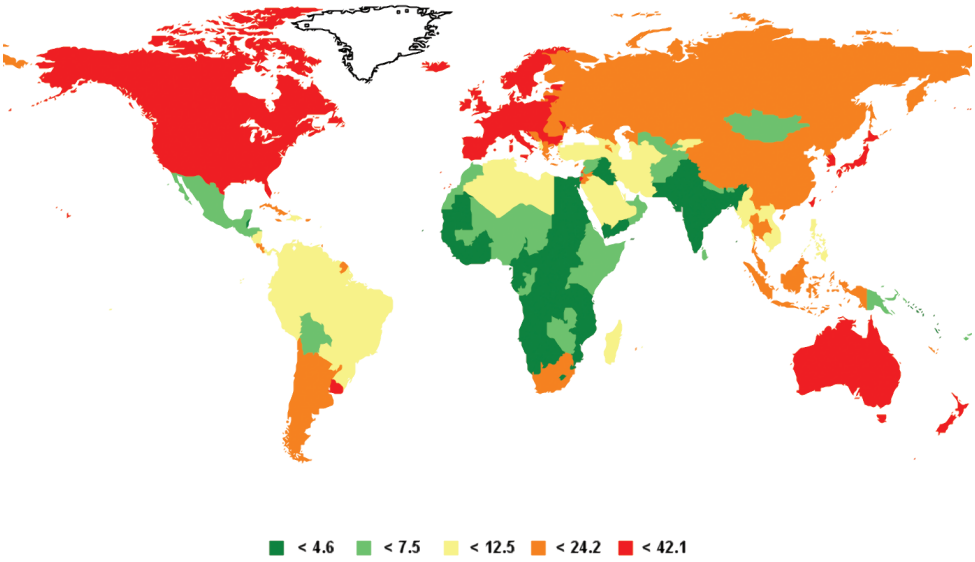


Figure 1-1. Worldwide colorectal cancer incidence per 100,000 persons per year.[1]

CRC incidence steeply increases with age, and it is higher in men than in women (Figure 1-2). At young ages, CRC is rare, and often associated with a genetic predisposition. In the US, the CRC incidence has been decreasing and is now lower than in the Netherlands.

In the Netherlands, the number of newly diagnosed CRC cases has increased to 12,000 per year, accounting for 5,000 deaths per year (Figure 1-3). This makes CRC the second leading cause of cancer death for men and the third for women in the Netherlands.[3]

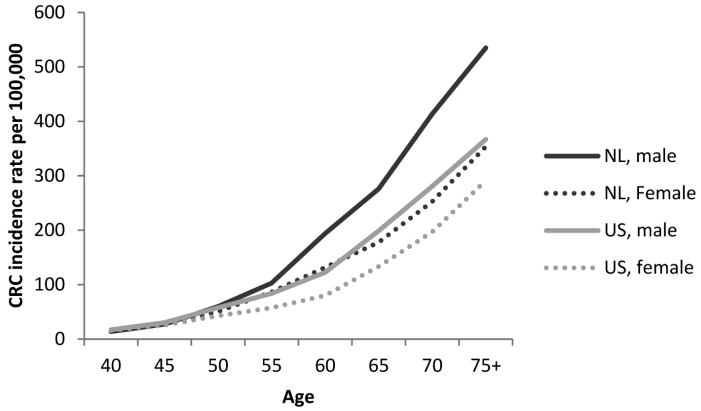


Figure 1-2. Colorectal cancer incidence by age and gender in the Netherlands (NL) and the United States (US), per 100,000 persons per year.[1]

Risk factors

The main risk factor for CRC is alcohol consumption (Table 1-1).[4] Other risk factors are red meat and processed meat consumption, diabetes, smoking and obesity.[4] Factors that have been identified as protective for CRC are physical activity,[4] vitamin D[5] and aspirin intake.[6] Aspirin intake was also preventive for the development of adenomas (RR 0.83 (0.72 – 0.96)).[7]

Individuals at increased risk for CRC due to the risk factors mentioned here are also at increased risk for a number of other diseases. Primary prevention by interventions that focus on changing the habits of these individuals is therefore important. Successful primary prevention would limit the importance of secondary prevention. However,

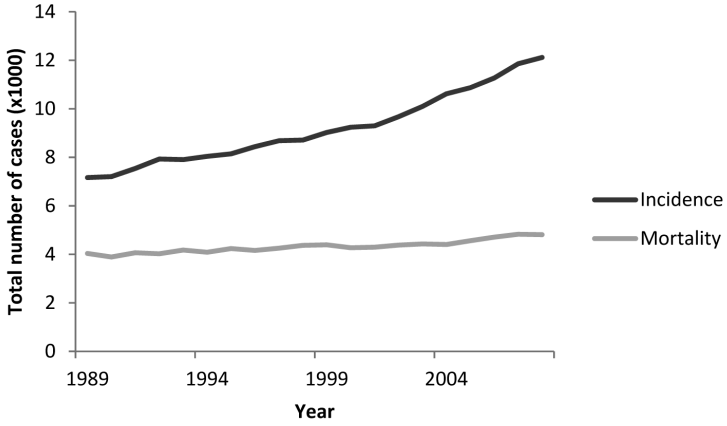


Figure 1-3. Yearly number of new CRC cases and CRC deaths in the Netherlands.

Table 1-1. Risk factors for colorectal cancer

Variable	Relative Risk (95% CI)
Alcohol	1.6 (1.4 – 1.7) [4]
Red meat	1.2 (1.1 – 1.3) [4]
Processed meat	1.2 (1.1 – 1.3) [4]
Diabetes	1.2 (1.2 – 1.3) [4]
Smoking	1.2 (1.1 – 1.2) [4]
Obesity	1.2 (1.1 – 1.3) [4]
Physical activity	0.8 (0.8 – 0.9) [4]
Vitamin D*	0.6 (0.4 – 0.8) [5]
Aspirins**	0.7 (0.6 – 0.9) [6]

* Odds Ratio
** Hazard Ratio

until now such interventions have not been successful enough to make secondary prevention unimportant. In this thesis, we will focus on secondary prevention by screening for early detection and treatment of colorectal cancer and its precursors.

NATURAL HISTORY

CRC includes all cancers that develop in the rectum, sigmoid colon, descending colon, ascending colon or cecum (Figure 1-4). Distal cancers develop in the rectum, sigmoid, or descending colon, while proximal cancers arise in the transverse or ascending colon, or

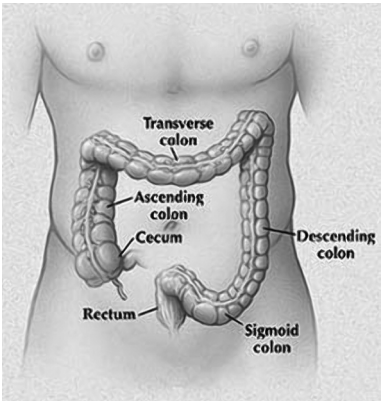


Figure 1-4. Sub localizations of the colorectum.

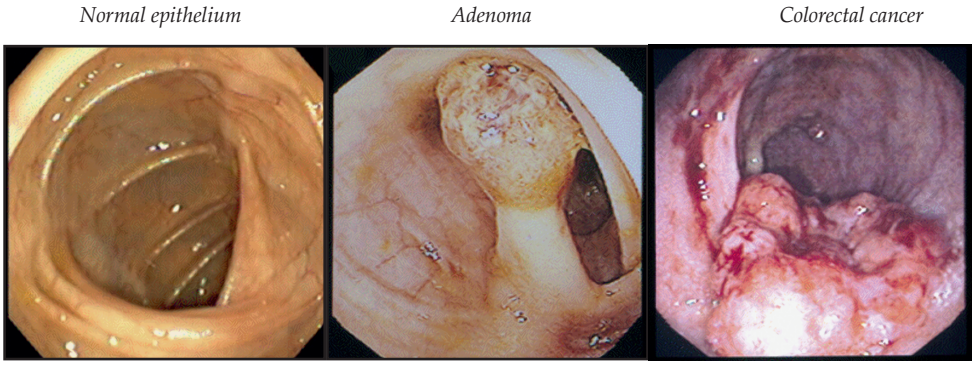


Figure 1-5. Natural history of colorectal cancer. Disease progresses from normal to adenoma, and finally to cancer.

in the cecum. These cancers are generally assumed to develop through the adenoma-carcinoma sequence.[8,9] Disease then progresses from normal, to adenoma and finally to cancer (Figure 1-5). In established market economies, adenomas are prevalent in approximately 40% of 60-year old men, and 29% of 60-year old women.[10] Adenomas usually do not cause symptoms, and most of them do not develop into cancer. Some adenomas become malignant, and will cause symptoms sooner or later. The cancer can be in a localized or advanced stage once it becomes symptomatic and is diagnosed in one of the stages I, II, III or IV. The estimated average duration of a cancer before it is diagnosed is almost 7 years.[11] The stage of diagnosis to a large extent determines the prognosis of disease. The relative survival after 5 years is 92% in stage I and 5% in stage IV (Table 1-2).

GENETICS

Approximately 2-5% of all CRC cases are associated with well-defined inherited syndromes including Familial Adenomatous Polyposis (FAP) and Hereditary NonPolyposis Colorectal Carcinoma (HNPCC or Lynch syndrom).[12] In individuals with these syndromes, CRC incidence often occurs before the age of 50. HNPCC is more common than FAP. The lifetime CRC risk of an individual with HNPCC is 50-80%.[12] Individuals with HNPCC sometimes develop more adenomas than average risk individuals, but the most important reason for their high CRC risk is that the adenomas are more aggressive. HNPCC related CRC develops relatively often at a proximal location.[12] FAP occurs in approximately one in 10,000 individuals. These individuals develop many adenomas,

Table 1-2. Stage distribution and 5-year relative survival of CRC diagnosed in 2000-2002 in the Netherlands.[3]

Stage	CRC diagnosed (%)	5-year relative survival (%)
I	19	92
II	35	75
III	26	55
IV	20	5

usually at a young age. Hundreds or even thousands of adenomas is not uncommon. When left untreated, CRC is inevitable, usually before the age of 50.[12]

A quarter of the CRC cases occur in individuals with relatives diagnosed with CRC, but without a known genetic predisposition. Approximately 15% of the individuals between ages 30 and 70 has at least one first degree relative with CRC.[13] They have approximately a twofold risk for CRC compared to individuals without a CRC family history.[14-16] The risk increases with the number of relatives diagnosed with CRC and with a younger age at CRC diagnosis of these relatives. There was no increased risk in spouses of CRC cases that had lived together for at least 30 years.[17] A study on twins indicated that at least 35% of all colorectal cancers is associated with hereditary factors.[18] Screening is in general more successful when the preclinical screen detectable disease develops slowly. For individuals with a family history without known genetic disorders it is not known if the increased CRC risk is caused by more adenomas which however have the usual long average duration, or by a more aggressive development of the adenomas. In case of more adenomas, it is easier to prevent cancer by detection and removal of the adenomas.

SCREENING

As already mentioned, CRC can be prevented by the detection and removal of its precursor, the adenoma. But early detection of the cancer itself can also significantly reduce CRC mortality because of the much better relative survival in early stage compared to advanced stages. Several screening tests are available that can detect preclinical CRC and sometimes also adenomas. The tests can be divided into the categories stool tests, endoscopy tests and imaging tests.

There are three types of stool tests, namely the guaiac fecal occult blood test (gFOBT), the immunochemical FOBT or Fecal immunochemical test (FIT), and the stool DNA test.

Table 1-3. Evidence on mortality reduction from gFOBT randomized trials (intention-to-screen-analysis).

Trial	Period	Age group	Mean follow-up (years)	Screening interval	Relative mortality risk ratio (95% CI)
UK [20, 21]	1981-1991	45-74	11	2	0.87 (0.78-0.97)
Denmark [22, 23]	1985-2002	45-75	17	2	0.89 (0.78-1.01)
US [24, 25]	1976-1977	50-80	18	2	0.79 (0.62-0.97)
Sweden [26]	1982-1990	60-64	15.5	2	0.84 (0.71-0.99)
US [24, 25]	1976-1977	50-80	18	1	0.67 (0.51-0.83)

gFOBT detects any blood, while the FIT detects specifically human blood. The stool DNA test detects DNA markers associated with colorectal neoplasia.

Several randomized controlled trials of gFOBT have shown a mortality reduction of 13-33% (Table 1-3). Individuals performed a home-based Hemoccult II test, consisting of two samples from each of three consecutive bowel movements. The six samples led to a positive or negative overall test result. Individuals with a positive test result were referred to colonoscopy. Based on these RCTs, the sensitivity for CRC was estimated at 51% in the stage that the CRC would have become clinical, and 19% in earlier stages.[11] Hemoccult Sensa is a more recent guaiac based test. It is more sensitive but less specific than Hemoccult II.[19]

Evidence from RCTs on the effectiveness of FIT screening is lacking. Case-control studies suggested a mortality reduction from CRC of 50-80%.[27,28] Another study showed a higher sensitivity for advanced neoplasia (adenomas of 10 mm or more, adenomas with more than 25% villous component or high-grade dysplasia, and cancers) of FIT compared to gFOBT.[19] Several quantitative FIT tests have been developed. Individuals are referred to colonoscopy if the level of hemoglobin in their stool is higher than a pre-specified cutoff level. Some studies showed a higher sensitivity for FIT compared to gFOBT at cutoff levels with a similar specificity.[29,30] Recently, in the Netherlands trials have been undertaken to compare gFOBT (Hemoccult II) with FIT at different cutoff levels in a randomized population-based setting, inviting 30,000 individuals aged 50-74. Individuals that were invited for gFOBT screening in these trials were asked to collect from 3 bowel movements, while FIT was performed on 1 stool only. Collecting from more than one stool might also be useful for FIT if cancers bleed intermittently. The comparison of sampling from 1 or 2 stools was also assessed in these trials, and the results will be discussed later in this thesis.

The stool DNA test is a relatively new test that has not yet proven to reduce mortality from CRC.

Table 1-4. Evidence on mortality reduction from once-only flexible sigmoidoscopy randomized trials (intention-to-screen analysis).

Trial	Period	Age group	Mean follow-up (years)	Relative risk ratio (95% CI)
UK [31]	1994-1999	55-64	11	0.69 (0.59-0.82)
Norway [32]	1999-2000	55-64	6	0.73 (0.47-1.13)
Italy [33]	1995-1999	55-64	11	0.78 (0.56-1.08)

With endoscopy testing the colorectum is inspected by inserting a flexible tube with an optic camera. Adenomas and cancers can be detected, and adenomas can be removed during the same procedure. The most frequently used techniques are flexible sigmoidoscopy and colonoscopy. With flexible sigmoidoscopy only the distal part of the colon can be inspected. The sensitivity for both adenomas and cancer is high within the reach of the test. The mortality reduction shown in three RCTs was 22%-31% (Table 1-4). There are no results from randomized controlled trials of colonoscopy, although two trials have recently started. The multicentre Nordic-European Initiative on Colorectal Cancer (NORDICC) randomizes individuals to colonoscopy or no screening, and the Spanish trial randomizes individuals to FIT or colonoscopy (www.clinicaltrials.gov). Colonoscopy is the test with the highest risk for serious complications, sometimes even fatal. This is one of the reasons why colonoscopy is not recommended for screening average risk individuals in most European countries. Another reason is a too small capacity for screening the general population by colonoscopy. In some countries, the colonoscopy capacity is even too small for the further diagnosis of the positives of a full scale FOBT screening program. The optimal FOBT screening program in case of a limited colonoscopy capacity needs to be further explored.

A recent promising imaging technique for CRC screening is Computed Tomography Colonography, which enables the visualization of the whole colorectum. Evidence on the mortality reduction is lacking. The sensitivity and specificity have shown to be comparable to that of colonoscopy. Individuals with advanced lesions should undergo a colonoscopy in order to have the lesion removed. There is debate on whether or not individuals with small polyps should be referred to colonoscopy.

Population based screening

The European Health Council recommends FOBT screening for average risk individuals in the age group 50-75.[34] FIT is the preferred test because of its proven better test characteristics compared to gFOBT.[34] By the end of 2007, ten EU Member States were

Table 1-5. CRC screening recommendations of USPSTF for average risk individuals in the US[38]

Test	Screening Interval
FOBT (FIT or Sensa)	1
Flexible Sigmoidoscopy	5
Colonoscopy	10
CTC*	5
Fecal DNA*	Not specified

* USPSTF concludes there is insufficient evidence to assess benefits and harms of these tests as screening modalities[38]

in the process of implementing national population based CRC screening programmes: Cyprus, Finland, France, Hungary, Italy, Poland, Portugal, Romania, Slovenia and the United Kingdom.[35] Furthermore, seven Member States had established nationwide non-population-based programmes. In the meantime, ten Member States have newly established or have upgraded their existing CRC screening programmes (Czech Republic, France, Ireland, Lithuania, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom).[34] Most of the countries use gFOBT, FIT is used in Italy and Australia.[36,37] Some of these countries also use endoscopy as a screening test, and Poland has a program with colonoscopy only. In the Netherlands, the decision has been made only very recently to start a nationwide CRC screening program. Screening will be implemented stepwise to be able to build up colonoscopy capacity in the meantime. Eventually, individuals aged between 55 and 75 will be invited every 2 years to perform a FIT, and individuals with a hemoglobin level of 50 ng/ml or more will be referred to colonoscopy.

In the United States, individuals older than age 50 are recommended to undergo CRC screening.[38,39] One of the guidelines recommends against routine screening after age 75.[38] The frequency depends on the test used (Table 1-5).

Population-based screening programs have individuals at average risk as their target population. Individuals at increased risk have their own guidelines, like for example individuals with a family history of CRC and no known genetic disorders. These individuals are recommended to undergo earlier or more frequent colonoscopy than average risk individuals. In the Netherlands, individuals are recommended to have a colonoscopy every 6 years starting at age 45 if they have a first degree relative (FDR) diagnosed before age 50, or if they have 2 or more affected FDRs. In the US, the recommended screening interval is 5 years starting at age 40 or ten years before the age of diagnosis of the FDR, for individuals with 1 FDR diagnosed before age 60, or with two or more FDRs.

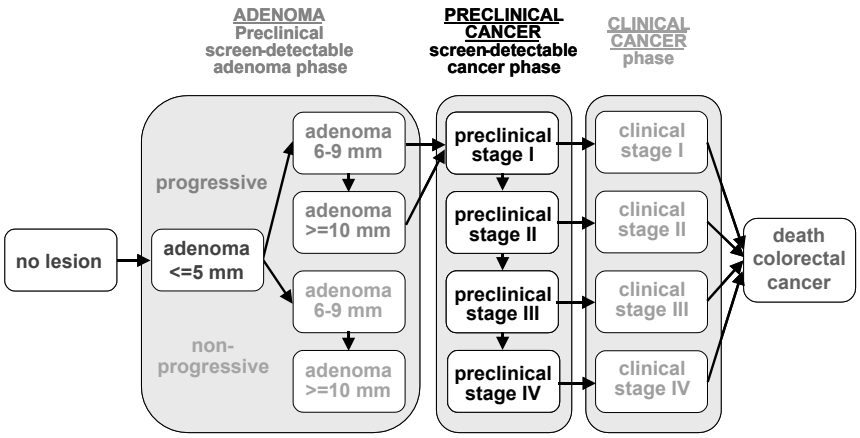


Figure 1-6. Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for CRC. Adenomas are categorized by size.

MISCAN

Mathematical models can be used to help policy makers in making decisions on how and when to screen for CRC. In this thesis we used the micro-simulation model Miscan-Colon to assess the costs and health effects of CRC screening. The MISCAN-Colon model was developed at the Department of Public Health at Erasmus MC, The Netherlands, in collaboration with the U.S. National Cancer Institute to assess the effect of different interventions on the occurrence of CRC in a population. The model simulates individuals from birth to death, first without screening and subsequently with the changes that would occur under the implementation of a screening program. In every individual, adenomas can arise and some of them will develop into cancer. A schematic representation of the natural history as used in the model is given in Figure 1-6.

Adenomas are initially small (1-5mm) and progress to medium (6-9mm) and large (10+mm). The majority of adenomas is assumed to be non-progressive and will never develop into cancer. The progressive adenomas have the ability to become cancer but not all of them will make it to cancer in an individual's lifetime. The adenomas that do become malignant, transform into stage I cancers and will progress into stages II, III and IV, unless diagnosed earlier. The survival after clinical diagnosis depends on the age and the cancer stage at diagnosis. Screening can result in a gain in life-years when

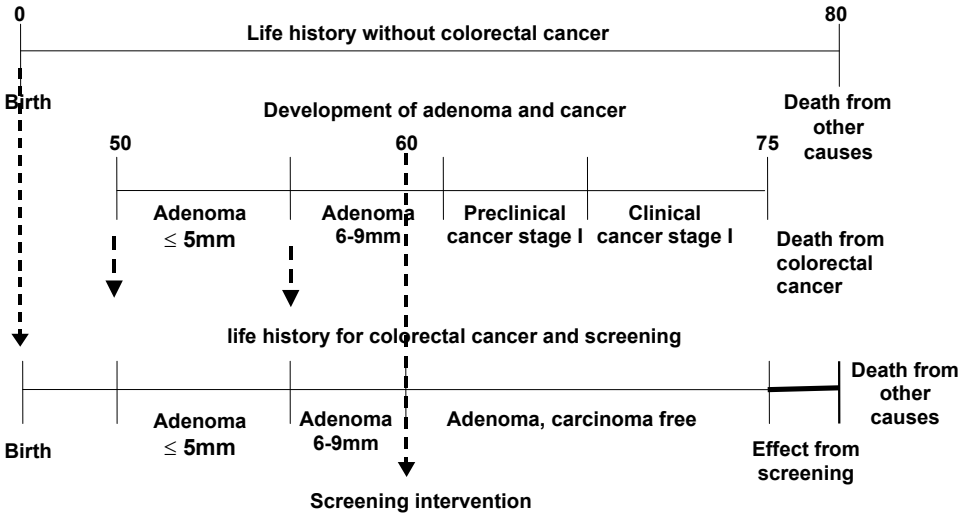


Figure 1-7. Modeling natural history and screening into life history

cancers are detected and treated at earlier stages or when adenomas are detected and consequently removed before they became cancer.

Figure 1-7 shows an example of how an individual is simulated in Miscan-Colon. A time of birth and a time of death is generated first, resulting in the life history without CRC shown in the top line. The individual in the example dies at age 80 from other causes. Subsequently adenomas are simulated for that individual. For many individuals no adenomas are generated, for others one or more. In the example in figure 1-7, the person gets one adenoma at age 50 (2nd line in figure 1-7). The adenoma is progressive. After having grown to 6-9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms and diagnosis and eventually resulting in an earlier death from CRC, at age 75. After the simulation of the life histories in the situation without screening, the model can simulate the situation with screening. Adenomas can be detected and removed, preventing CRC incidence, and preclinical cancers can be found earlier improving an individual's survival. The probability that an adenoma or cancer is found depends on the sensitivity of the screening test. In the picture there is one screening, at age 60. At the screening, the adenoma is detected and removed, and the person therefore no longer develops cancer. This results in a combined life history for colorectal cancer and screening (bottom line). and therefore this individual no longer develops cancer. The person dies at the moment of death from other causes and the effect of screening is a gain of 5 life years, the difference in age at death between the situation

without screening and the situation with screening. Of course many less favorable examples are possible: a person could have developed new adenomas after the screening moment, or an adenoma could have been missed by the screening test. But in this case the individual really benefited from the screening intervention.

In this thesis, different versions of Miscan are used. The different model assumptions per chapter can be found in the appendix.

Cost-effectiveness analysis

Cost-effectiveness analysis is a standard decision support tool, estimating the incremental costs and health effects of an intervention compared to one or more alternatives. The interventions that we consider are screening strategies. The main components of a screening strategy are the ages when to start and stop screening, the interval between subsequent screenings, and the screening test that will be used. The health effects of a screening strategy are usually expressed in number of life-years gained or number of quality adjusted life-years gained. Costs of a screening strategy consist of extra costs for screening, diagnostic follow-up, surveillance, complications from screening and surveillance and savings from treatment. In assessing the screening strategies, those that are more costly and less effective than at least one other strategy are ruled out. This is called simple dominance. Strategies that are more costly and less effective than a mix of other strategies are also ruled out; this is called extended dominance. The remaining strategies are not dominated and are known as "efficient". On a plot of life-years gained versus costs, the line that connects the efficient strategies is called the efficient frontier, and all dominated strategies lie below this line. The incremental cost-effectiveness ratio (ICER) of an efficient strategy is determined by comparing its costs and effects to those of the next less costly and less effective efficient strategy. The ICER increases with an increasing effectiveness and all strategies with an ICER under a chosen acceptability threshold value have enough health effects to justify the additional costs. The strategy with an ICER closest to the threshold is the most effective amongst these strategies and would be the most reasonable choice. Based on such an analysis, decisions can be made on when to start and stop screening, the screening interval and the type of screening test to use. The cost-effectiveness of screening depends on the background risk of the population. In individuals with a CRC family history for example, more effects will be achieved with CRC screening at about the same costs. As a result, a more intensive screening strategy will be chosen when using the same cost-effectiveness threshold value as used for the average risk population.

Research questions and outline of this thesis

The goal of this thesis is to assess the health effects and costs of several colorectal cancer screening strategies in individuals with and without a family history of the disease. More specifically, we addressed the following research questions:

- How do attendance rates and test characteristics of guaiac and immunochemical fecal occult blood testing for colorectal cancer compare? (*Chapter 2*)
- What is, in a colorectal cancer screening program with a fecal immunochemical test, the appropriate cutoff level for referral to colonoscopy and what are the optimal screening ages? (*Chapter 3*)
- How should screening with a fecal occult blood test be adjusted in order to deal with a limited colonoscopy capacity? (*Chapter 4)*
- How do attendance and test characteristics of 2-sample screening from different stools with a fecal immunochemical test compare with those of 1-sample screening? (*Chapter 5*)
- Are individuals with a family history of colorectal cancer at increased risk for developing colorectal adenomas, besides their increased risk for cancer? (*Chapter 6*)
- What are optimal colonoscopy screening policies for individuals with varying family histories of colorectal cancer? (*Chapter 7, Chapter 8*)

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

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Abstract

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

INTRODUCTION

Colorectal cancer (CRC) is a major health problem in the Western world. Screening can reduce CRC mortality due to detection of early carcinomas and removal of pre-malignant lesions.[1,2] The American Gastroenterology Association,[3] the US Multi-Society Task Force,[4] Asia Pacific Working Group on Colorectal Cancer screening[5] and the European council[6] recommend CRC screening for average risk individuals over 50 years of age. Several countries have a nation-wide screening programme mainly based on guaiac-based faecal occult blood test (gFOBT), as this is the only available test with a proven mortality reduction,[7-9] but consider changing to an immunochemical FOBT (FIT) programme based on accumulating evidence that FIT is superior to gFOBT screening, including a higher attendance[10-12] and detection rate[11,13,14], as well as a higher sensitivity without a significant drop in specificity.[13,15-19] Furthermore, FIT specifically binds human haemoglobin (Hb), which makes drugs and diet restrictions superfluous.

Immunochemical faecal occult blood testing samples can be analysed automatically, which has important advantages for reproducibility, quality control, capacity, and thus personnel need and costs.[19,20] Another advantage of FIT is the quantitative test results, which allows determining an optimal cutoff value for a nation-wide screening programme.[13,18,19,21,22] The cutoff value for a positive test can be based on a positivity rate that meets the available colonoscopy resources. At the same time, the number of colonoscopies is an important determinant of the neoplasia detection rate, and thus of the potential preventive effect of a CRC screening programme.

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

MATERIALS AND METHODS

Study population

The study was performed in the Rijnmond region in the southwest of the Netherlands. This region includes Rotterdam and surrounding villages and harbours 338 000 inhabitants in the target population. The region thus combines both rural

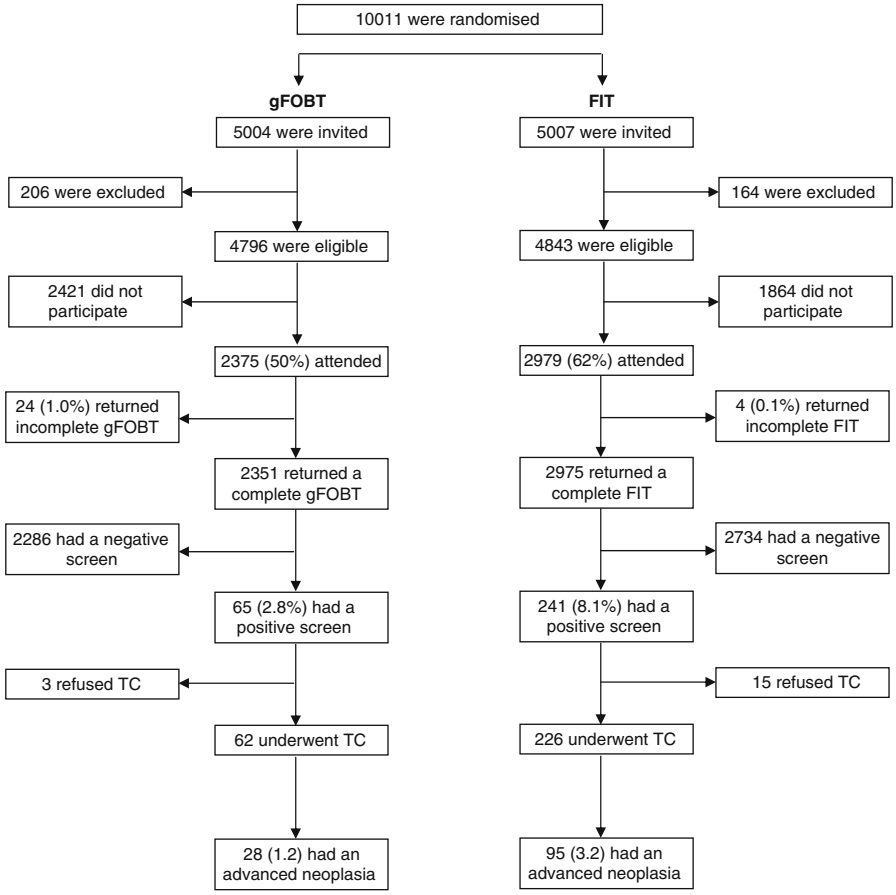

Figure 2-1. Trial profile. gFOBT: guaiac-based faecal occult blood test; FIT: immunochemical faecal occult blood test; TC: total colonoscopy.

and urban settings. Ten thousand and eleven individuals, aged 50 – 74 years, were randomly selected from the municipal registries. The selected individuals were 1 : 1 randomised per household after stratifying for age, sex and social economic status into group A (gFOBT) or B (FIT) using a computer-generated allocation algorithm (Tenalea, Amsterdam, The Netherlands) (Figure 2-1). Randomisation occurred before invitation. Informed consent was asked after randomisation. Individuals with a history of inflammatory bowel disease or CRC, a colonoscopy, sigmoidoscopy or barium contrast enema in the last 3 years, major health problems or inability to sign informed consent were excluded. Recruitment took place between November 2006 and November 2007.

Interventions

The randomly selected 10 011 individuals were sent a pre-invitation letter containing information on CRC screening. Two weeks later, an invitation letter was sent with information on possible advantages and risks of screening. This was accompanied by an informed consent form that had to be signed and returned. A test set was sent along with the invitation. A reminder was sent 6 weeks afterwards to all non-respondents. Information about the study was further given by direct visits of research physicians to all general practitioners (GPs) in the region, as well as through a dedicated website (www.dikkedarmkankerpreventie.nl), mailings and information sites of the municipality offices, regional newspapers, and national and regional broadcasting.

Group A: gFOBT

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

Group B: immunochemical FOBT

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

Follow-up

In case of a negative gFOBT or FIT, both the GP and the participant were informed by mail within 3 weeks. No further follow-up was necessary. In case of a positive gFOBT or FIT (faecal Hb level $\geq$ 50ng/ml), the GP was informed both by telephone and mail within 2 weeks. The GP informed the participant about the test result and referred the participant for colonoscopy. A colonoscopy was scheduled within 2 weeks after the screening test results had become available.

Colonoscopy

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

Ethical approval

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

Statistical analysis

Differences in proportions between screening strategies were calculated using a χ^2 test. Differences in means between screening strategies were calculated using a Student's *t*-test. All P-values were two-sided and considered significant if < 0.05. Uni- and multivariate logistic regression analyses were used to determine the influence of sex and age on positivity rate, number needed to scope (NNscope), detection rate and number needed to screen (NNscreen). The positivity rate was defined as the proportion of participants having a positive gFOBT or FIT test. For FIT, the positivity rate was separately calculated for cutoff levels of 50, 75, 100, 125, 150, 175 and 200 ng/ml, respectively. The detection rate was defined as the proportion of participants having advanced neoplasia. This was calculated as the number of screenees with an advanced neoplasia divided by all screenees with a complete screening test. Advanced neoplasia included CRC and advanced adenoma. Advanced adenoma was defined as adenoma $\geq$ 10 mm or with a histology showing either a $\geq$ 25% villous component or high-grade dysplasia. We compared faecal Hb measurements between screenees with a normal colonoscopy and screenees with non-neoplastic polyps, non-advanced adenomas and advanced adenomas and CRC as the most advanced lesion by the Kruskal-Wallis non-parametric analysis of variance and the Mann-Whitney test, as the data were not normally distrib-

uted. Participation, positivity and detection rate, positive predictive value (PPV) and specificity were calculated and described as percentages with 95% confidence intervals (95% CI). The specificity for advanced neoplasia and CRC was calculated under the rare disease assumption as the ratio of the number of all negative screenees and the total number of screenees subtracted by the number of true positives.[23] Number needed to scope describes the number of colonoscopies to find one screenee with an advanced neoplasia or CRC. Number needed to screen was calculated as the number of complete screening tests needed to find one advanced neoplasia or CRC. Differences in PPV between sexes or age groups in the FIT arm were described for a cutoff of 100 ng/ml, as this cutoff value is most commonly used.[11,21,24]

Results

In total, 10 011 subjects were randomised before invitation to one of the two FOBTs. Three hundred and seventy (3.7%) subjects were excluded from analyses (332 subjects met one of the exclusion criteria, 26 had moved away and 12 had died). A total of 2375 out of 4796 (50%; 95% CI: 48–51%) participants attended gFOBT screening. The gFOBT was analysable in 2351 cases (99%). In all, 2979 out of 4843 (62%; 95% CI: 60 –63%) subjects attended FIT screening and the test was complete in 2975 subjects (99.9%) (Figure 2-1). The distribution of age (mean ± s.d. gFOBT 61 ± 7 years; FIT 61 ± 7 years old) and sex (male gFOBT 46%; FIT 48%) of the analysable subjects did not differ between the two screening arms.

Proportion of positive tests

In total, 65 screenees had a positive gFOBT (2.8%; 95% CI: 2.2 – 3.6%). Immunochemical faecal occult blood testing was positive in 241 screenees (8.1%; 95% CI: 7.2 – 9.1%) at a cutoff of 50 ng/ml and in 103 screenees (3.5%; 95% CI: 2.9 – 4.2%) at a cutoff of 200 ng/ml (Table 2-1). A significant decrease in the proportion of positive tests was seen between cutoff values of 50 and 75 ng/ml (8.1 *vs* 5.7%), followed by a more gradual decrease between cutoff values of 75 and 200 ng/ml (Table 2-1). Male screenees were more likely to have a positive gFOBT than female screenees (3.7 *vs* 1.9%; OR: 1.4; CI: 1.1 – 1.8) or FIT (FIT100: 6.8 *vs* 3.0%; OR: 2.3; 95% CI: 1.6 – 3.3). The proportion of positive gFOBTs was slightly higher in screenees aged 60 – 74 years than in screenees aged 50 – 59 years, but this difference was not significant (3.1 *vs* 2.3%; OR: 1.3; 95% 0.8 – 2.2). In the FIT arm, the proportion of positive tests was significantly higher in screenees aged 60 – 74 years than in screenees aged 50 – 59 years (FIT^{100}: 6.1 *vs* 3.3%; OR: 1.8; 95% 1.3 – 2.6) (Figure 2-2).

Table 2-1. Test characteristics of gFOBT and FIT at different cutoff levels

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

CRC = colorectal cancer; FIT = immunochemical faecal occult blood test; gFOBT = guaiac-based faecal occult blood test; NNscope = number needed to scope to detect one screenee with an advanced neoplasia; NNscreen = number needed to screen to detect one screenee with an advanced neoplasia; PPV = positive predictive value; TC = total colonoscopy. *P <0.05 compared with gFOBT; advanced neoplasia: adenoma ≥ 10 mm, villous component (≥ 25% villous) or high-grade dysplasia; CRC.

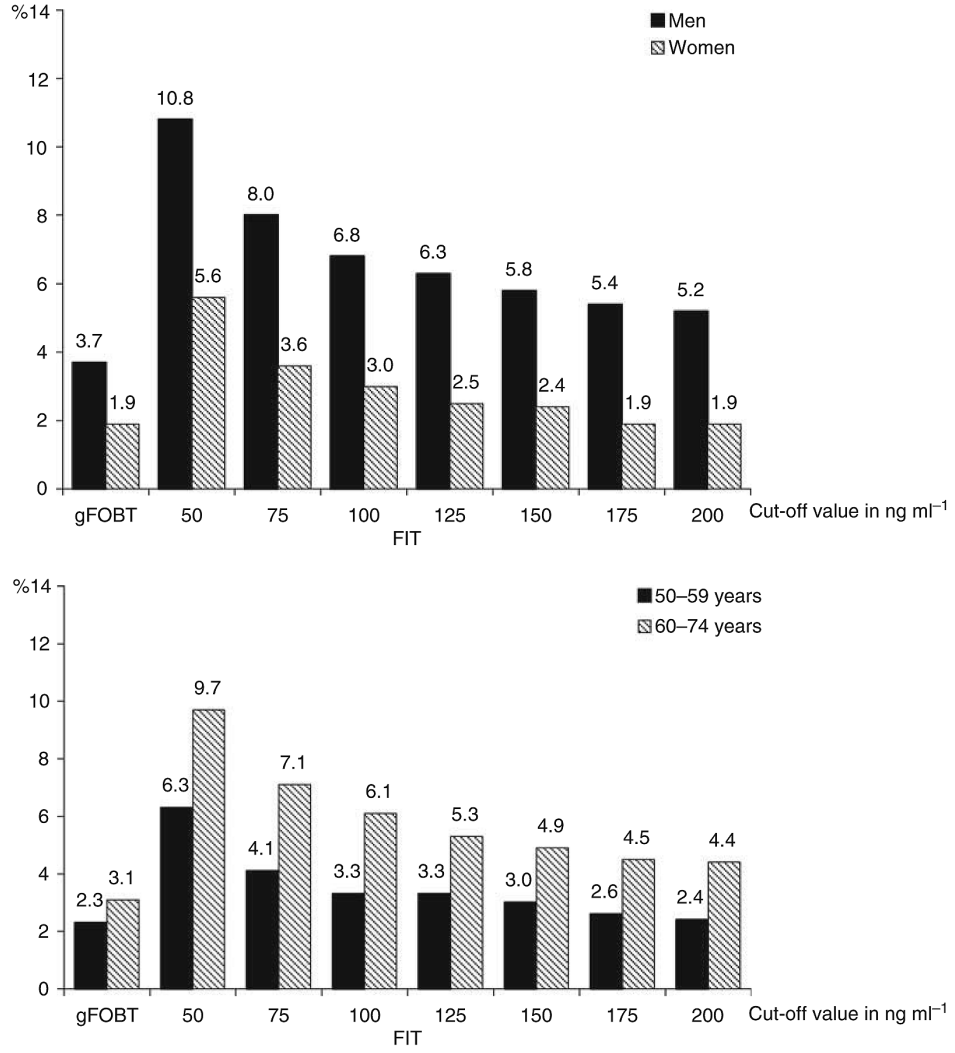

Figure 2-2. Positivity rate of gFOBT and FIT at different cutoffs in men and women aged 50–59 and 60–74 years.

Colonoscopy findings per test and cutoff value

Sixty-two (95.4%) of the 65 gFOBT-positive screenees and 226 (93.8%) of the 241 screenees with a FIT result ≥ 50 ng/ml underwent a colonoscopy. A double-contrast barium enema was performed in three subjects with an incomplete colonoscopy. Two colonoscopies were incomplete due to an obstructing tumour. The colonoscopy findings are in Table 2-2 and are related to the amount of Hb in the faeces. A significantly higher proportion

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

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

CRC = colorectal cancer; FIT = immunochemical faecal occult blood test. Advanced adenoma: adenoma ≥ 10 mm, villous component (≥ 25% villous) or high-grade dysplasia; CRC.

of screenees with faecal Hb levels of 150 – 200 (47%) and ≥ 200 (61%) had advanced neoplasia than screenees with faecal Hb levels of 50 – 150 ng (25%) ($P = 0.009$ and $P < 0.001$, respectively), whereas the proportions were similar among screenees with values of 50 – 100 ng/ml and 100 – 150 ng/ml (25 *vs* 18%; $P = 0.60$).

Haemoglobin levels per finding

The median faecal Hb level of positive screenees with a normal colonoscopy was 50 ng/ml. Median Hb measurement in screenees with, as the most advanced finding, a non-neoplastic polyp was 94 ng/ml, with a non-advanced adenoma was 112 ng/ml, with an advanced adenoma was 373 ng/ml and with a CRC was 404 ng/ml. Faecal Hb levels of screenees with a normal colonoscopy did not significantly differ from those of screenees with non-neoplastic ($P = 0.88$) or non-advanced adenoma ($P = 0.89$), whereas the faecal Hb level of screenees with an advanced adenoma or CRC was significantly higher than that of screenees with a normal colonoscopy (both $P < 0.001$). The difference in fecal Hb level between those with advanced adenoma and those with CRC was not significant ($P = 0.53$).

Test characteristics

The PPV of gFOBT for advanced neoplasia and for CRC was 45% (95% CI: 33 – 58%) and 10% (95% CI: 4 – 20%), respectively. Immunochemical faecal occult blood testing showed a more favourable PPV for detecting advanced neoplasia at higher cutoff values

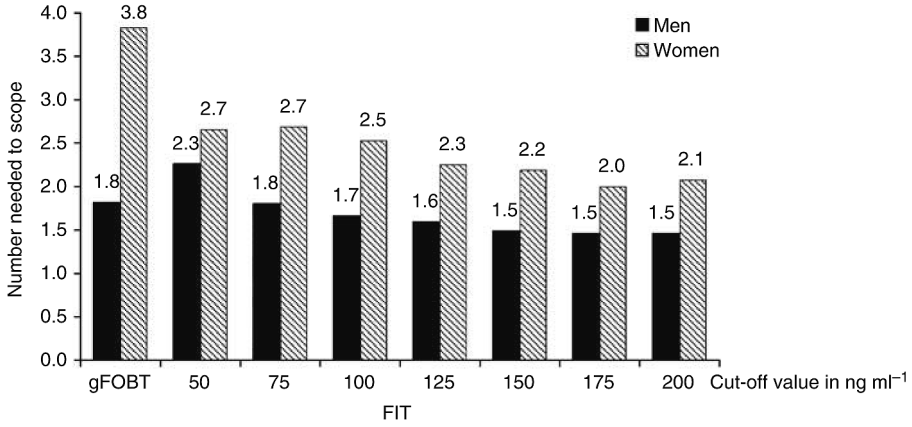

Figure 2-3. Numbers needed to scope to find one screenee with an advanced neoplasia in men and women at different cutoff values.

(Table 2-1), but this difference was only significant at cutoff values ≥ 175 ng/ml (gFOBT 45% *vs* FIT^{175} 63%; $P = 0.029$ and FIT^{200} 62%; $P = 0.035$). The PPV for CRC was similar for gFOBT and FIT at all cutoff levels, although the PPV of FIT steadily increased with increasing cutoff value (Table 2-1).

The NNscope to detect one screenee with an advanced neoplasia or CRC was 2.2 and 10.3, respectively, for gFOBT. The corresponding numbers with FIT screening were 2.4 and 14.1 at 50 ng/ml and 1.6 and 8.2 at 200 ng/ml cutoff values (Table 2-1) for advanced neoplasia and CRC, respectively. Men showed a lower NNscope for advanced neoplasia than women (gFOBT men: 1.8; women: 3.8; $P = 0.04$; FIT^{100}: 1.7; women: 2.5; $P = 0.03$) (Figure 2-3). No differences in NNscope for advanced neoplasia or CRC were seen between different age groups (gFOBT, $P = 0.33$; FIT^{100} $P = 0.81$).

The estimated specificity for not having advanced neoplasia and CRC was significantly lower for FIT at cutoff values ≤ 100 ng/ml than that for gFOBT (Table 2-1). Above a cutoff value of 100 ng/ml, the estimated specificity was similar to that of gFOBT.

Detection rate

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

Male sex was associated with a higher detection rate of advanced neoplasia in both screening arms (gFOBT: OR 4.2; 95% CI: 1.7 – 10.4; FIT^{100}: OR 3.5; 95% CI: 2.0 – 6.1).

Screenees aged 60 – 74 years showed a higher detection rate of advanced neoplasia than screenees aged 50 – 59 years in the FIT arm (FIT^{100}: OR 1.9; 95% CI: 1.2 – 3.2), whereas no significant difference between both age groups was found in the gFOBT arm (OR 1.5; 95% CI: 0.7 – 3.3).

The NNscreen to find at least one advanced neoplasia was favourable at all cutoff levels for FIT compared with the gFOBT arm (Table 2-1). Male screenees showed significantly lower numbers needed to screen to detect one advanced neoplasia than female screenees (gFOBT: men: 57 *vs* women: 181; $P = 0.002$; FIT 100^{100}: men: 26 *vs* women: 91; $P < 0.001$).

DISCUSSION

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

Furthermore, FIT testing provides quantitative results, which allows the determination of an optimal cutoff value for a nation-wide screening programme based on colonoscopy capacity and the intended detection rate in the screened population. A low cutoff value (50 ng/ml) provided not only a high detection rate of advanced neoplasia, but also more false-positive test results and thus a higher number of unnecessary colonoscopies. False-positive results are associated with anxiety[25] and increased costs.[26] Increasing the cutoff value resulted in a decrease in detection rate but a more favourable PPV. The key question is at which cutoff value the magnitude of benefits (possible the early detection of CRC or the removal of adenomas) is sufficient to outweigh the harms (burden, complications, demand on colonoscopy capacity and costs of screening). The cutoff at which this trade-off becomes acceptable must be determined in a full cost-effectiveness analysis. However, the ratio between detection rate and NNscope to find one screenee with an advanced neoplasia is a good indicator for this trade-off, as it reflects both benefit (detecting an advanced neoplasia) and harm (the need to undergo colonoscopy). We found that the NNscope was higher with FIT than with gFOBT screening when using an FIT cutoff of 50 ng/ml, but this changed in favour of FIT when increasing the

cutoff to 75 ng/ml (Table 2-1). At a cutoff value of 75 ng/ml, the detection rate with FIT was two-fold higher than that with gFOBT. At the same time, increasing the FIT cutoff from 50 to 75 ng/ml had a considerably stronger limiting effect on the proportion of FIT positives (falling from 8.1 to 5.7%) than any other similar further increase of the FIT cutoff (Table 2-1). Further increasing the cutoff level from 75 to 100 ng/ml would result in a larger decline in detection rate (8.8%) than in NNscope (7.3%) and therefore a less favourable trade-off (Table 2-1). For these reasons, we conclude that FIT provided the most optimal trade-off when using a cutoff value of 75 ng/ml. This conclusion is in agreement with observations from a colonoscopy study determining the onetime sensitivity and specificity of the same OC-Micro Latex FIT test in a population of individuals at higher risk for CRC.[19] The latter study and our results come to a lower cutoff than the recommended cutoff value of 100 ng/ml by the manufacturer (Eiken Chemical Co.) and by an earlier study examining the performance of the OC-Sensor at different cutoff levels.[27]

Our findings on positivity rate, PPV and the detection rate of CRC at a cutoff value of 100 ng/ml are in agreement with those of other studies using the OC-Sensor with this specific cutoff.[11,21,27-29] Both our study and a similarly designed study by van Rossum *et al*,[11] however, found a significantly higher PPV and detection rate for advanced neoplasia (PPV: 52 – 53%; DR: 2.4 – 2.5%) than other studies (PPV: 20 – 39%; DR: 0.8 – 1.2%),[21,27-29] even though these studies all focused on the same age group and applied the same test and definition of advanced neoplasia. A possible explanation is that both Dutch studies were carried out in a screening-naive population, whereas other studies from Italy and France were performed in parallel to a nation-wide programme and therefore were more likely to have included subjects screened earlier with a lower risk on advanced neoplasia.[21,27-29]

The positivity rate is the main driver for the number of colonoscopies among attendants. In countries with a gFOBT screening programme, changing to FIT screening with a 50 ng/ml cutoff value would require a considerable (gFOBT: 2.8% *vs* FIT[50] 8.1% positivity rate) increase in colonoscopy capacity for screening. This effect is augmented by a higher attendance rate to FIT than to gFOBT screening.[11,12] Thus, FIT screening enables a more efficient screening with increased participation[10-12] and improved test performances[11,13,14,16,30,31], potentially allowing a decrease in screening intensity by lengthening the screening interval.

The detection rate of advanced neoplasia was significantly higher in men than in women in both screening arms. Likewise, the NNscreen to detect an advanced neoplasia was lower in men than in women. Similar differences in detection rates for advanced neoplasia between both sexes were found in two colonoscopy screening studies.[32-34]

Furthermore, the CRC incidence rates are on an average 1.5 times higher in men than in women aged 50 – 75 years.[1,35] Thus, the higher pre-test probabilities for advanced neoplasia in men explain this difference. Several studies have, therefore, suggested to develop sex-specific recommendations for CRC screening.[36,37] A differentiated approach taking sex and potentially age into account would be relatively easy with FIT screening. One could argue to use different cutoff values for men and women to achieve a similar NNscope, which would result in a considerable higher cutoff value for women than for men (Figure 2-3).

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

In conclusion, this randomised population-based trial provides important data on the test characteristics of FIT screening at different cutoff values. Immunochemical faecal occult blood testing is considerably more effective than gFOBT within the complete range of tested cutoff values. From our experience, a cutoff value of 75 ng/ml provided an adequate positivity rate and an acceptable trade-off between detection rate and NNscope to find a screenee with an advanced neoplasia. Increasing the cutoff value can be considered in case of insufficient colonoscopy capacity, at the cost of a gradual decrease in detection rate. The optimal cutoff value within a specific population can be based

on a local screening programme, taking major determinants into account, including the incidence of neoplasia, the intended screening interval, colonoscopy capacity and cost efficacy. With this in mind, the use of variable cutoffs for different sub-groups is a further option for individualised CRC screening.

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3

Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening

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Abstract

Background & Aims: Two European randomized trials (n = 30,000) compared guaiac fecal occult blood testing (gFOBT) with quantitative fecal immunochemical testing (FIT) and showed better attendance rates and test characteristics for FIT. We aimed to identify the most cost-effective FIT cutoff level for referral to colonoscopy based on data from these trials and allowing for differences in screening ages.
Methods: We used the validated MIcrosimulation SCreening ANalysis (MISCAN)-Colon micro-simulation model to estimate costs and effects of different screening strategies for FIT cutoff levels of 50, 75, 100, 150 and 200 ng hemoglobin/ml. For each cutoff level, screening strategies were assessed with various age ranges and screening intervals. We assumed sufficient colonoscopy capacity for all strategies.
Results: At all cost levels, FIT screening was most effective with the 50 ng/ml cutoff level. The incremental cost-effectiveness ratio (ICER) of biennial screening between ages 55 and 75 using FIT at 50 ng/ml, for example, was 3,900 euro per life-year gained. Annual screening had an ICER of 14,900 euro per life-year gained, in combination with a wider age range (between ages 45 and 80 years). In the sensitivity analysis, 50 ng/ml remained the preferred cutoff level.
Conclusion: FIT screening is more cost-effective at a cutoff level of 50 ng/ml than at higher cutoff levels. This supports the recommendation to use FIT at a cutoff level of 50 ng/ml, which is considerably lower than the values used in current practice.

Introduction

Randomized controlled trials have shown that population-based screening for colorectal cancer (CRC) with fecal occult blood tests (FOBT) reduces CRC mortality by 15 to 33%.[1-3] These trials have been performed with the Hemoccult II test, a guaiac-based FOBT (gFOBT). Fecal immunochemical tests (FIT) have become available more recently. In the United States, Hemoccult II is no longer recommended but is replaced by more sensitive FOBTs, in particular the FIT. So far, most of the (European) countries with a national screening program use gFOBT[4] because of its proven effectiveness and cost-effectiveness[5] and limited colonoscopy requirements. In the Netherlands, two trials randomized individuals aged 50 to 74 to a gFOBT (Hemoccult II, Biopharma, Weesp, the Netherlands) or a quantitative FIT (OC-Hemodia Latex, Eiken, Tokyo, Japan).[6,7] FIT proved superior to gFOBT because of its higher attendance, better test characteristics,[6-8] and similar costs.[9] Because the FIT is a quantitative test, it is possible to choose the cutoff level for referral to colonoscopy. The cutoff level recommended by the manufacturer is 100 ng hemoglobin/ml. A lower cutoff value means a gain in sensitivity and a loss in specificity. In both trials the FIT cutoff level used for colonoscopy referral was set low at 50 ng/ml. Based on the trial results, we performed a cost-effectiveness analysis to compare FIT at different cutoff levels (50 ng/ml and greater), varying the screening interval and the age range of the target population. For this analysis, we used the validated micro-simulation model MISCAN-Colon.

Patients and Methods

MISCAN-Colon

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

on the stage specific survival and, again, owing to competition from causes of death other than CRC. This completes the life history without screening. The same life history is subsequently simulated with screening, where adenomas and CRC can be detected and subsequently removed. In this way, CRC incidence or CRC death can be prevented. For the situations without and with screening, the life-years lived are aggregated over the total simulated population. The life-years gained by screening are calculated as the difference between these totals.

The model reproduced the Dutch population age distribution as it was in 2005 (Statistics Netherlands, www.cbs.nl), with the cancer incidence as observed in the Netherlands from 1999 to 2003 (Comprehensive Cancer Center, www.ikcnet.nl). Survival after clinical diagnosis of a cancer was based on relative survival data from 1985 to 2004 from the south of the Netherlands,[13] since national data were not available. The survival for individuals aged 75 or older was adjusted to fit the observed age-increasing mortality/incidence ratio (Comprehensive Cancer Center).

The validity of the model has been successfully tested on the results of large screening and surveillance studies, such as the randomized FOBT trials in Minnesota, Funen and Nottingham,[14] the CoCap sigmoidoscopy study,[10] and the National Polyp Study.[15] Finally, the model was able to explain observed incidence and mortality trends in the US when accounting for risk factor trends, screening practice and chemotherapy treatment.[16]

Test Characteristics

We simulated FIT at different cutoff levels for referral to colonoscopy by assuming a specific sensitivity and specificity per cutoff level. Test characteristics were fitted to the positivity and detection rates as observed in the first screening round of the Dutch trials[6-8, 17] (Tables 3-1 and 3-2). We assumed that the probability that a CRC bleeds and thus the sensitivity of FIT for CRC depends on the time until diagnosis, in concordance with the findings for gFOBT which were based on a calibration of the MISCAN-Colon model to three FOBT-trials.[14] In that analysis, the rates of screen-detected CRC and interval CRC observed in the FOBT-trials were better simulated by using this assumption than by two other hypotheses: sensitivity is the same for all preclinical CRC stages, and sensitivity increases with each stage. This result is to be expected when cancers that bleed do so increasingly over time, starting "occultly" and ending as clinically visible. This interpretation also holds for FIT. Colonoscopy sensitivity was assumed 75% for adenomas of 1-5 mm, 85% for adenomas of 6-9 mm, and 95% for adenomas of 10+ mm and CRC.[18]

Screening Strategies

We simulated screening in the Dutch population over a period of 30 years starting in

Table 3-1. Model assumptions: test characteristics of FIT at cutoff levels 50, 75, 100, 150 and 200 ng/ml based on the observed positivity and detection rates in Table 3-2.

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

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

** The sensitivity for CRC depends on CRC stage as it was assumed higher in the stage that the CRC would have become clinical in the situation without screening than in earlier stages.

2005, with each test modality using a total of 48 combinations of the following: age to start screening, 45, 50, 55, and 60 years; age to stop screening, 70, 75, and 80 years; screen interval 1, 1.5, 2, and 3 years. After a positive FIT result a diagnostic colonoscopy was offered. If no adenomas were found during the colonoscopy, the individual was offered another FIT after 10 years, the interval recommended after a negative test result with primary colonoscopy screening. If one or more adenomas were found during the colonoscopy, the adenomas were removed and the individual entered surveillance

Table 3-2. Simulated (observed) positivity rates and detection rates per 100 screened individuals (highest grade finding per individual) for FIT at cutoff levels 50, 75, 100, 150 and 200 ng/ml in the first screening round of the Dutch trials.[6-8,17]

Test	Positivity rate	No neoplasia despite FIT result above cutoff level	Non advanced adenomas	Advanced adenomas*	CRC
FIT 200	3.7 (3.7)	1.3 (1.3)	0.48 (0.48)	1.54 (1.54)	0.39 (0.39)
FIT 150	4.4 (4.4)	1.6 (1.6)	0.59 (0.58)	1.78 (1.82)	0.40 (0.40)
FIT 100	5.3 (5.3)	2.1 (2.1)	0.83 (0.80)	1.98 (2.01)	0.42 (0.42)
FIT 75	6.4 (6.4)	2.7 (2.7)	0.99 (1.02)	2.30 (2.27)	0.45 (0.45)
FIT 50	8.4 (8.4)	3.6 (3.7)	1.57 (1.54)	2.73 (2.71)	0.48 (0.48)

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

according to the Dutch guidelines,[19] with another colonoscopy recommended after 6 years in the case of 1 or 2 adenomas and after 3 years in the case of 3 or more adenomas. We assumed that surveillance stopped at the age of 80 years, the oldest stop age for screening.

Attendance

We initially simulated all strategies assuming 100% attendance for FIT, and for diagnostic and surveillance colonoscopies. To assess the strategies and their cost-effectiveness level in a realistic situation, we used observed attendance rates, namely 60% attendance for FIT, and 85% for diagnostic colonoscopy.[6,7] Attendance to surveillance colonoscopy was assumed 80%.[20] Based on gFOBT trials, we assumed that 10% of the individuals never attended FOBT screening.[21] They had a higher risk for CRC than the general population (RR=1.15).[1] For follow up rounds, we assumed that 80% of the individuals who attended the previous screening round, would attend again.[22]

Costs

In the base case analysis, we included screening and treatment costs as given in Table 3-3. Base case organizational costs for FIT screening were based on the Dutch cervical cancer screening program, adjusted for differences with FIT screening. Costs for the test kits were based on prices of the manufacturer. Costs for analysis of the tests consisted of costs for material and personnel needed during the process of registration, analysis and authorization of returned tests.[9] Colonoscopy costs were based on an internal six-month study at the Erasmus MC (data not shown). Costs for complications after colonoscopy were based on DBC-rates (Diagnosis Treatment Combination), derived from the Dutch Health Care Authority (http://ctg.bit-ic.nl/Nzatarieven/top.do).

Costs of CRC were divided into three clinically relevant phases of care: initial treatment, continuous care and terminal care. Initial treatment costs were based on DBC-rates, except for Oxaliplatin. The costs for Oxaliplatin were derived from the Dutch Health Care Insurance Board (www.medicijnkosten.nl). We assumed that during the continuous care phase, individuals followed the Dutch guidelines (www.oncoline.nl) and costs for periodic control were based on DBC-rates. Terminal care costs were based on a Dutch last year of life by cause of death analysis. These were estimated at €19,700 for patients that ultimately died of CRC.[23] We assumed that these costs increase with stage at diagnosis, at a rate observed for US patients.[24,25] Dutch terminal care costs for individuals who died of CRC were approximately 40% of the US costs. We assumed that terminal care costs of patients with CRC who died from other causes were also 40% of the US levels.

Table 3-3. Model assumptions of the base case and sensitivity analyses.

Variable	Base case analysis	Sensitivity analyses	
Quality of life loss			
Colonoscopy	–	1 day lost per colonoscopy	
*CRC from diagnosis onwards**	–	Per phase of care (1-utility) Initial treatment[34]: Stage I: 0.26 during one year Stage II: 0.3 during one year Stage III: 0.4 during one year Stage IV: 0.75 during one year Continuous care [35]: 0.15 in years in between initial and terminal phase Terminal care death by CRC: 0.75 in last year before dying of CRC Terminal care death by other cause: 0.35 in last year before dying of other causes	
Correlation FIT results	–	74% of the large adenomas (>9 mm) that are not detected, will not be detected in the next screening round [27]	
Surveillance	According to Dutch guidelines: 1 or 2 adenomas: 6-year interval >2 adenomas: 3-year interval	According to US guidelines: 1 or 2 adenomas 0-9 mm: 5-year interval >2 adenomas 0-9 mm: 3- year interval >1 adenomas 10+ mm: 3-year interval	
		Low value	**High value**
Fatal complications after colonoscopy	1 per 10,000 colonoscopies	No fatal complications	1 per 1,000 colonoscopies with polypectomy, 1 per 10,000 colonoscopies without polypectomy
FIT costs			
Costs per invitation (organization and test kit)	€14.85	50%	200%
Costs per attendee (personnel and materials for analysis)	€4.37		
Colonoscopy costs			
Without polypectomy	€303	50%	200%
With polypectomy	€393		
**Costs complications after colonoscopy ** **	€1,250	50%	200%
Treatment costs *			

	Initial treatment	Continuous care	Terminal care death CRC	Terminal care death other cause		
Stage I	€12,500	€340	€17,500	€4,400	50%	200%
Stage II	€17,000	€340	€17,500	€4,000		
Stage III	€21,000	€340	€18,500	€5,200		
Stage IV	€25,000	€340	€25,000	€14,000		

*CRC treatment was divided into three clinically relevant phases – initial, continuous and terminal care. The initial phase was defined as the first 12 months following diagnosis, the terminal phase was defined as the final 12 months of life, and the continuous phase was defined as all months between the initial and terminal phase. For patients surviving less than 24 months, the final 12 months were allocated to the terminal phase. The remaining months of observation were allocated to the initial phase.

** Assumed complication rate is 2.4 per 1,000 colonoscopies

Cost-effectiveness Analysis

For all screening strategies we used MISCAN-Colon to estimate costs and number of life-years gained due to screening compared to the situation without screening. Costs and life-years gained were discounted by 3% per year.[26] Strategies that were more costly and less effective than other strategies were ruled out by simple dominance. Strategies that were more costly and less effective than a mix of other strategies were ruled out by extended dominance. The remaining strategies are not dominated and are known as "efficient". On a plot of life-years gained versus costs, the line that connects the efficient strategies is called the efficient frontier, and all dominated strategies lie below this line. The incremental cost-effectiveness ratio (ICER) of an efficient strategy was determined by comparing its costs and effects with those of the next less costly and less effective efficient strategy.

Prevalence Screening

We compared the diagnostic yield and number needed to find one CRC during colonoscopy of FIT strategies (cutoff levels 50, 75, 100, 150 and 200 ng/ml) and the primary colonoscopy strategy, that is, referring every screenee to colonoscopy, which is equivalent to using a cutoff level of 0 ng/ml. To this end we simulated one screening round at age 65 years with 100% attendance for FIT and colonoscopy.

Sensitivity Analysis

We performed 13 sensitivity analyses on 7 parameters (Table 3-3) and the surveillance rules by using different assumptions than in the base case analysis. We adjusted for reduced quality of life due to screening as well as to CRC treatment. Correlated FIT results were assumed because lesions that did not bleed at the time of a screening round may have a higher than average probability of not bleeding in a next screening round too. We used the results of a population based screening program in Italy to estimate the correlation between false negative FIT results for cancers and advanced adenomas in subsequent screening rounds.[27] Ten sensitivity analyses resulted from evaluations of lower and higher values than in the base case for fatal complication rates and for costs of FIT, colonoscopy, complications and treatment. Finally, we assessed differences in outcomes if we assumed US surveillance guidelines, referring individuals with 1 or 2 adenomas 0-9 mm to colonoscopy after a 5-year interval and individuals with 3 or more adenomas 0-9 mm, or 1 or more adenomas 10+ mm to colonoscopy after 3 years. We decided not to perform a probabilistic sensitivity analysis after having weighed the limited added value against the computational effort required (see discussion).

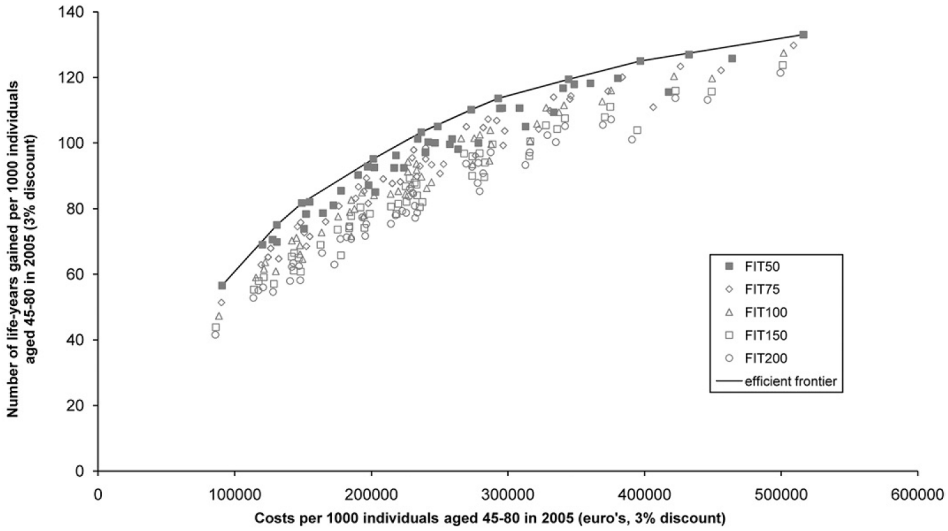

Figure 3-1. Costs and life-years gained (3% discount) per 1,000 individuals aged 45-80 years in 2005 of strategies varying by age to begin screening, age to end screening and screening interval for FIT 50-200 ng/ml, with 100% attendance. The efficient strategies are connected by the efficient frontier and are given in Table 4.

RESULTS

Cost-effectiveness Analysis

A FIT cutoff level of 50 ng/ml resulted in more life-years gained at the same or lower costs than higher cutoff levels (Figure 3-1). Consequently, the efficient frontier consisted of FIT 50 strategies only. The higher the cutoff level used, the further the strategies were situated below the efficient frontier (see Appendix Table 3-1 for detailed results on costs and effects for all cutoff levels).

The costs and life-years gained of the efficient strategies under the assumption of 100% attendance are given in Table 3-4. The incremental costs per life-year gained of screening with FIT 50 were always less than €20,000. The ICER of the most costly strategy, annual screening between ages 45 and 80 years, was €14,900 per life-year gained compared to screening every 1.5 years in the same age range. Biennial screening was efficient with an age range of 55 to 75 years, as well as with an age range of 50 to 80 years. These strategies had an ICER of €3,900 and €5,800 per life year gained respectively.

Table 3-4. Efficient screening strategies in case of 100% attendance. All efficient strategies use FIT with cutoff level 50 ng/ml. Costs and life-years gained per 1,000 individuals aged 45-80 years in 2005 (3% discount).

begin - end age (y) / interval (y) / no. of screens	Costs (€)	Life-years gained	ICER (€)**
60-69 / 3 / 4*	91,000	57	1,600
55-70 / 3 / 6	131,000	75	2,200
55-73 / 3 / 7*	149,000	82	2,800
55-75 / 2 / 11*	201,000	95	3,900
55-74.5 / 1.5 / 14*	237,000	103	4,300
55-79 / 1.5 / 17*	273,000	110	5,300
50-80 / 2 / 16	293,000	114	5,800
50-80 / 1.5 / 21	344,000	119	8,900
45-79.5 / 1.5 / 24	397,000	125	9,400
45-80 / 1 / 36*	515,000	133	14,900

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

** The ICER compares the costs and life-years gained of every efficient strategy to the next less costly efficient strategy

Effect of Attendance Rate

When we assumed observed attendance rates (60% for FIT and 80% for diagnostic colonoscopy), FIT 50 was also the efficient choice. Due to non-attendance, both costs and life-years gained decreased (Table 3-5). Compared with the situation with full attendance, the efficient strategies shifted towards shorter intervals between the screening rounds. The shorter screening intervals thus compensated for suboptimal attendance.

Prevalence Screening

The diagnostic yield of screening at age 65 years was 0.56 if everyone was referred to colonoscopy (equivalent to a FIT cutoff level of 0 ng/ml, see Figure 3-2). The yield decreased to 0.42 for FIT 50, and further to 0.34 for FIT 200. The number needed to scope to detect one CRC decreased more rapidly, from 106 to 14 colonoscopies, when changing from FIT 0 to FIT 50, and then further to 8 colonoscopies when FIT 200 was used.

Sensitivity Analyses

The optimality of a cutoff level of 50 ng/ml for FIT proved to be robust for alternative model assumptions. Only if colonoscopy costs doubled did higher cutoff levels become efficient next to the 50 ng/ml cutoff. This assumption also resulted in the highest ICER values, €10,800 per life-year saved for biennial screening between ages 50 and 80 years and €26,600 for annual screening between ages 45 and 80 years. The ICER-values for

Table 3-5. Efficient screening strategies in case of observed attendance[a]. All efficient strategies use FIT with cutoff level 50 ng/ml. Costs and life-years gained per 1000 individuals aged 45-80 years in 2005 (3% discount).

begin - end age (y) / interval (y) / no. of screens	Costs (€)	Life-years gained	ICER (€)[c]
60-69 / 3 / 4[b]	76,000	35	2,100
60-70 / 2 / 6	106,000	47	2,600
55-73 / 3 / 7[b]	127,000	53	3,400
55-69 / 2 / 8	138,000	56	3,400
55-75 / 2 / 11[b]	180,000	68	3,600
55-74.5 / 1.5 / 14[b]	215,000	77	4,100
55-79 / 1.5 / 17[b]	252,000	84	4,900
55-80 / 1 / 26	337,000	95	7,700
50-80 / 1 / 31	415,000	104	8,400
45-80 / 1 /36[b]	493,000	109	16,100

a Observed attendance rates: 60% for FIT, 85% for diagnostic colonoscopy and 80% for surveillance colonoscopy
b This strategy is both efficient for 100% and for realistic attendance
c The ICER compares the costs and life-years gained of every efficient strategy to the next less costly efficient strategy.

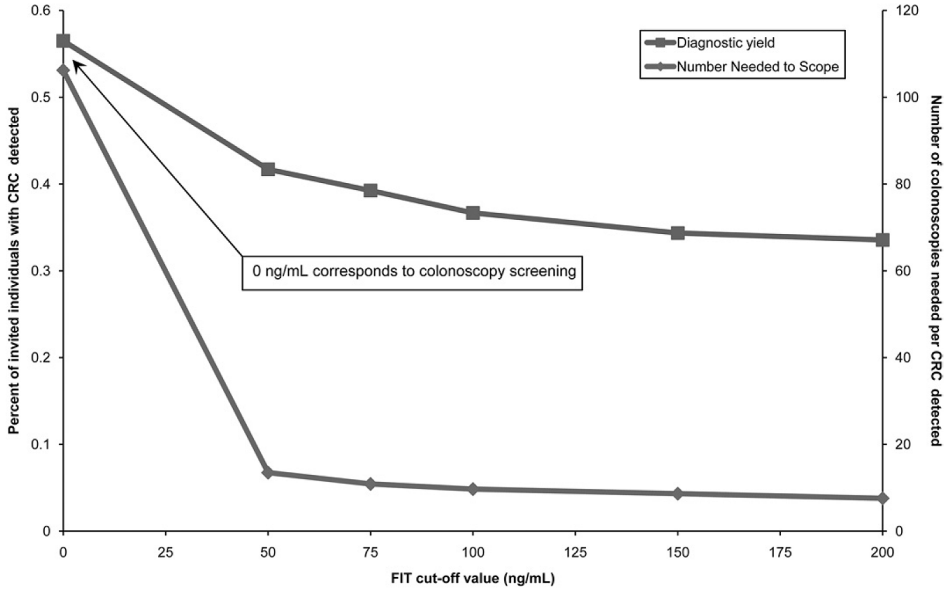

Figure 3-2. Diagnostic Yield and Number Needed to Scope for CRC when individuals aged 65 are screened once with a FIT at cutoff levels 0-200 ng/ml

quality adjusted life-years (qaly) gained were very similar to those for unadjusted life-years gained and ranged from €1,800 per quality-adjusted life years gained for screening every 3 years between ages 60 and 69 years, to €13,500 for annual screening between ages 45 and 80. Thus, the quality loss because of screening and follow-up was balanced by a quality gain because of fewer individuals with CRC.

Discussion

Our study shows that within the range analyzed (50-200 ng/ml), the optimal cutoff level for FIT screening with the quantitative OC-Sensor is 50 ng/ml. The cutoff level of 50 ng/ml has the highest sensitivity and lowest specificity. The decreased specificity of screening with FIT 50 was outweighed by the fact that it needed fewer rounds compared with screening with higher cutoff levels, to be equally effective.

A one-way sensitivity analysis to evaluate the impact of uncertain parameters showed that the choice of 50 ng/ml was robust. We did not perform a probabilistic sensitivity analysis. Given the large number of strategies that has to be evaluated for each draw, such an analysis would require a huge computational effort. We believe that simulating all these varying strategies is one of the strengths of this analysis, because we were primarily interested in the comparison of different FIT cutoff levels allowing different screening frequencies and ages for each cutoff level. This is important, given that different test-characteristics may imply different optimal screening ages and may perform differently at different total cost levels. Besides, data on which to base the probability distributions of most of the parameters are lacking, which makes the interpretation of a probabilistic sensitivity analysis difficult, and the outcome of limited added value. One of the most uncertain assumptions of the model is that all CRCs arise from adenomas. For FIT screening, this assumption is probably not so critical because FIT has a low sensitivity for adenomas. Besides, by using an exponential distribution, the model generates many adenomas with relatively short durations that will not be detectable until shortly before becoming cancer even with repeated endoscopy screening. The possibility of the existence of never-bleeding adenomas, not detectable by FIT, was evaluated in the sensitivity analysis. We did not vary the parameters that describe the Dutch population because the results will be applicable to populations with similar CRC incidence and mortality, like many North American and West-European countries, assuming US surveillance instead of Dutch surveillance rules did not change the optimality of FIT 50.

Other investigators also discussed the best cutoff level of the FIT used in this analysis. In Italy, the recommendation was 100 ng/ml. However, only cutoff levels of 100 ng/ml

and greater were analyzed.[28] In a study in Taiwan, individuals with a test result less than 100 ng/ml were followed up for two years, and sensitivity was estimated for various cutoff levels based on interval cancers.[29] The authors concluded that 110 ng/ml should be the preferred cutoff level. However, the estimated costs were lowest at a cutoff value of 40 ng/ml, while the estimated number of life-years gained decreased from 40 ng/ml to higher cutoff levels (see Figure 3-4a in the study by Chen[29]). From a cost-effectiveness point of view, the cutoff of 40 ng/ml should therefore be preferred to higher cutoff values, which is consistent with our results. In a Japanese study, workers were offered colonoscopy above a cutoff level of 50 ng/ml.[30] The authors recommend a cutoff level of 200 ng/ml based on leveling off of the Receiver Operator Curve and minimal costs per CRC case detected in one screening round. The considerable savings in treatment costs were however not taken into account. Otherwise, a lower optimal cutoff level would have been obtained. Studies based on the same data that we used recommended a cutoff level of 75 ng/ml.[6, 17] This value was obtained with the criterion that no more than two individuals need to undergo colonoscopy to detect one individual with advanced neoplasia, motivated by the burden from colonoscopy and limited colonoscopy capacity.

When using the observed attendance rates (60% for FIT, 85% for colonoscopy after a positive FIT), the optimal cutoff level for FIT remained 50 ng/ml. Because most of the individuals do not attend all screening rounds, shorter intervals between screening rounds tend to become somewhat more cost-effective in the case of observed compared with complete attendance rates. The shorter intervals are not necessarily optimal for individuals who attend to every screening round. For that reason we also considered 100% attendance, identifying optimal strategies for individuals who follow the recommendations. For strategies that figure in both scenarios, the incremental cost-effectiveness levels were approximately the same.

Several other FOBTs are currently being used for CRC screening. The guaiac-based Hemoccult II test is used in several European screening programs and the Hemoccult Sensa is one of the recommended tests in the United States.[31] Randomized controlled trials have shown that FIT is superior to Hemoccult II because of the higher attendance rates, better test characteristics[6-8] and similar costs.[9] With the same specificity, the sensitivity of FIT is 1.5 times higher for CRC than the sensitivity of Hemoccult II. Hemoccult Sensa has a similar sensitivity as FIT but the lack of specificity is 3 times as high.[32] The test costs and laboratory requirements and procedures for both Hemoccult tests are similar. These similar costs, but higher specificity make FIT the preferred test over Hemoccult Sensa.

FIT selects individuals at risk for neoplasia to undergo a colonoscopy. Lowering the cutoff value means that more individuals, on average at lower risk, will be referred to colonoscopy. We could not analyze the cost-effectiveness of referring individuals with

a FIT result less than 50 ng/ml because these individuals were not referred in the trials. However, in the theoretical situation of a 0 ng/ml FIT cutoff level, everyone would be referred to colonoscopy. We showed that the number needed to scope (NNS) to detect a CRC decreases when we varied the cutoff value from 0 (primary colonoscopy screening) to 50 ng/ml (Figure 3-2). Using FIT 50 therefore still largely differs from offering everyone colonoscopy. Colonoscopy is more costly and more invasive than FIT, but can be performed with much larger intervals. A full analysis of health effects and cost-effectiveness comparing colonoscopy and FIT is beyond the scope of this article. The NNS further decreases with higher cutoff values, showing that the number of CRC detected per colonoscopy increases with higher cutoff values.

In this analysis, we assumed sufficient colonoscopy capacity for any of the considered screening programs. However, the introduction of a colorectal cancer screening program in a thus far unscreened population, as expected in the Netherlands for example, will require considerable expansion of the colonoscopy capacity. The colonoscopy requirement of most of the strategies in this analysis, in particular those with low cutoff levels, considerably exceed the colonoscopy capacity available in many countries.[33] Ideally, for a nationwide screening program one would aim to expand colonoscopy capacity over time to permit the use of preferred low cutoff FIT in the long term, while introducing the program gradually.

In conclusion, this analysis strongly supports the use of FIT at a low cutoff value for referral to colonoscopy for population-based FOBT CRC screening programs. Colonoscopy capacity could be gradually expanded to a level that permits the use of such a low FIT cutoff value.

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Appendix Table 3-1. Summary results of efficient strategies per cutoff level

Efficient strategies (Begin-end age/ interval/ # screens)	Incidence reduction (0% discount)	Mortality reduction (0% discount)	Life-years gained per 1000 individuals (3% discount)	Costs per 1000 individuals (× *1000* €) (3% discount)						
				Total	FOBT	Diagnostic colonoscopy after pos FOBT	Surveillance colonoscopy	Clinical diagnostic colonoscopy	Complications after colonoscopy	Treatment CRC
FIT 50										
60-69 / 3 / 4	7.1%	14.0%	57	91	46	70	68	-6.2	1.1	-89
55-70 / 3 / 6	9.7%	18.0%	75	131	69	96	98	-7.8	1.6	-126
55-73 / 3 / 7	10.3%	20.0%	82	149	76	108	104	-8.8	1.7	-132
55-75 / 2 / 11	12.7%	23.5%	95	201	109	144	127	-10.3	2.2	-171
55-74.5 / 1.5 / 14	14.4%	25.4%	103	237	132	165	150	-10.8	2.6	-202
55-79 / 1.5 / 17	14.8%	27.4%	110	273	147	186	152	-12.0	2.8	-202
50-80 / 2 / 16	14.3%	27.7%	114	293	150	188	154	-12.2	2.8	-189
50-80 / 1.5 / 21	16.3%	29.4%	119	344	185	219	175	-12.8	3.3	-224
45-79.5 / 1.5 / 24	17.2%	29.9%	125	397	217	243	191	-12.9	3.7	-244
45-80 / 1 / 36	19.2%	31.6%	133	516	288	300	222	-13.5	4.5	-285
FIT 75										
60-69 / 3 / 4	5.6%	12.4%	51	90	47	55	54	-5.7	0.9	-62
55-70 / 3 / 6	7.8%	16.0%	68	126	71	76	79	-7.1	1.3	-94
55-69 / 2 / 8	9.6%	17.7%	76	148	93	92	95	-7.7	1.5	-126
55-75 / 2 / 11	10.6%	21.6%	89	196	114	116	106	-9.7	1.8	-132
55-74.5 / 1.5 / 14	12.3%	23.6%	98	231	140	135	127	-10.4	2.2	-162
55-79 / 1.5 / 17	12.5%	25.8%	105	270	156	152	129	-11.5	2.3	-158
50-80 / 2 / 16	12.0%	25.9%	107	285	158	152	128	-11.6	2.3	-143
50-80 / 1.5 / 21	14.0%	27.7%	114	333	197	179	149	-12.4	2.7	-182
45-79.5 / 1.5 / 24	15.0%	28.5%	120	384	233	198	163	-12.6	3.0	-200
45-80 / 1 / 36	17.0%	30.6%	130	509	316	250	194	-13.3	3.7	-241

Efficient strategies (Begin-end age/ interval/ # screens)	Incidence reduction (0% discount)	Mortality reduction (0% discount)	Life-years gained per 1000 individuals (3% discount)	Costs per 1000 individuals (× *1000* €) (3% discount)						
				Total	FOBT	Diagnostic colonoscopy after pos FOBT	Surveillance colonoscopy	Clinical diagnostic colonoscopy	Complications after colonoscopy	Treatment CRC
FIT 100										
60-69 / 3 / 4	4.9%	11.4%	47	88	48	47	48	-5.3	0.8	-50
55-70 / 3 / 6	6.9%	14.8%	64	122	72	64	70	-6.7	1.1	-79
55-73 / 3 / 7	7.3%	16.8%	70	142	80	73	75	-7.7	1.2	-80
55-70 / 1.5 / 11	10.3%	19.4%	83	185	124	97	106	-8.4	1.7	-135
55-75 / 2 / 11	9.5%	20.5%	85	193	117	100	95	-9.4	1.6	-111
55-74.5 / 1.5 / 14	11.2%	22.6%	94	227	145	116	115	-10.0	1.9	-141
55-79 / 1.5 / 17	11.4%	24.8%	101	266	162	132	117	-11.3	2.0	-136
50-80 / 1.5 / 21	12.7%	26.8%	111	328	205	154	135	-12.1	2.4	-157
45-79.5 / 1.5 / 24	13.7%	27.5%	116	376	242	170	148	-12.3	2.6	-175
50-80 / 1 / 31	15.0%	28.9%	120	422	282	193	162	-12.9	2.9	-205
45-80 / 1 / 36	15.9%	30.1%	127	502	336	215	180	-13.2	3.3	-219
FIT 150										
60-69 / 3 / 4	4.2%	10.4%	44	86	48	40	41	-4.9	0.6	-39
60-69 / 1.5 / 7	6.7%	14.1%	58	118	81	60	63	-6.4	1.0	-81
55-69 / 2 / 8	7.4%	15.2%	66	144	97	66	74	-6.9	1.1	-88
55-75 / 2 / 11	8.2%	19.2%	80	192	120	85	83	-9.0	1.4	-89
55-74.5 / 1.5 / 14	9.7%	21.2%	89	228	149	100	102	-9.6	1.6	-114
55-79 / 1.5 / 17	9.8%	23.5%	97	268	167	114	103	-10.9	1.7	-107
55-80 / 1 / 26	12.2%	26.2%	108	342	238	146	122	-11.9	2.2	-155
45-79.5 / 1.5 / 24	11.9%	26.1%	111	375	250	145	130	-11.9	2.3	-142
50-80 / 1 / 31	13.5%	27.7%	116	423	295	167	144	-12.6	2.6	-173
45-80 / 1 / 36	14.3%	29.0%	124	501	351	186	160	-12.9	2.9	-186
FIT 200										
60-69 / 3 / 4	3.7%	9.8%	42	86	49	35	36	-4.7	0.6	-30
60-69 / 1.5 / 7	5.9%	13.3%	55	117	82	52	56	-6.1	0.9	-68
55-69 / 2 / 8	6.5%	14.4%	63	143	98	57	66	-6.6	1.0	-73
55-75 / 2 / 11	7.2%	18.4%	77	193	122	75	74	-8.7	1.2	-70
55-74.5 / 1.5 / 14	8.7%	20.4%	86	228	152	87	92	-9.4	1.4	-95
55-75 / 1 / 21	10.9%	22.8%	97	287	216	112	110	-10.4	1.8	-142
55-80 / 1 / 26	11.0%	25.4%	105	342	246	129	112	-11.8	1.9	-134
50-80 / 1 / 31	12.2%	26.9%	114	423	304	146	132	-12.5	2.3	-150
45-80 / 1 / 36	13.1%	28.2%	121	499	364	162	147	-12.8	2.5	-163

4

Fecal occult blood testing when colonoscopy capacity is limited

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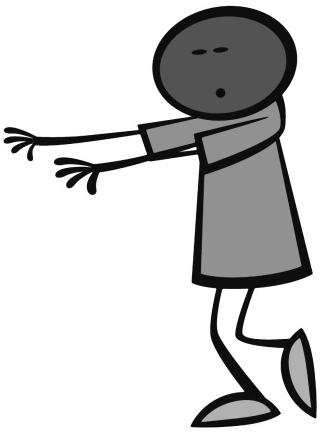

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Abstract

Background: Fecal occult blood testing (FOBT) can be adapted to a limited colonoscopy capacity by narrowing the age range or extending the screening interval, by using a more specific test or hemoglobin cutoff level for referral to colonoscopy and by restricting surveillance colonoscopy. Which of these options is most clinically effective and cost-effective has yet to be established.

Methods: We used the validated MISCAN-Colon micro-simulation model to estimate the number of colonoscopies, costs and health effects of different screening strategies using guaiac FOBT or fecal immunochemical test (FIT) at various hemoglobin cutoff levels between 50 and 200 ng haemoglobin/ml, different surveillance strategies, and various age ranges. We optimized the allocation of a limited number of colonoscopies on the basis of incremental cost-effectiveness.

Results: When colonoscopy capacity was unlimited, the optimal screening strategy was to administer on annual FIT with a 50 hemoglobin ng/ml cutoff level in individuals aged 45 to 80 years and to offer colonoscopy surveillance to all individuals with adenomas. When colonoscopy capacity was decreasing, the optimal screening adaptation was to first increase the FIT hemoglobin cutoff value to 200 ng/ml and narrow the age range to 50-75 years, to restrict colonoscopy surveillance, and finally to further decrease the number of screening rounds. FIT screening was always more cost-effective compared with gFOBT. Doubling colonoscopy capacity increased the benefits of screening up to 100%.

Conclusion: FIT should be used at higher hemoglobin cutoff levels when colonoscopy capacity is limited compared with unlimited and is more effective in terms of health outcomes and cost compared with gFOBT at all colonoscopy capacity levels. Increasing the colonoscopy capacity substantially increases the health benefits of FIT screening.

Introduction

Screening with a guaiac fecal occult blood test (gFOBT) has been proven to reduce mortality from colorectal cancer (CRC).[1-3] The ability of a screening program to have an impact at the population level depends on attendance at all screening rounds and diagnostic yield (the proportion of individuals found with adenomas or CRC). For that reason, recent studies have raised considerable interest in screening with fecal immunochemical testing (FIT), as it had been shown to increase attendance as well as diagnostic yield compared with the conventional gFOBT.[4-7] Another advantage of the quantitative FIT is that it enables the choice of a hemoglobin cutoff level for referral to colonoscopy. However, using FIT *vs* gFOBT in a screening program may be associated with a substantial demand for colonoscopies, especially when low hemoglobin cutoff levels are being used.

Currently, colonoscopy capacity is limited in many countries,[8-10] and waiting times for a colonoscopy of up to 12 weeks have been reported.[11] Colonoscopy capacity cannot be increased overnight and screening programs should be adjusted to the available capacity, at least temporarily. The limited capacity was an important consideration in various countries, such as Canada, Finland and the United Kingdom (UK), in which screening programs that had a relatively low impact on colonoscopy capacity were started. Most countries have limited the colonoscopy demand by using the highly specific guaiac based FOBT,[12-14] sometimes focusing on populations with narrow age restrictions such as 60-69 years[13,14] whereas both the European Union Council and the Public Health Agency of Canada recommend FOBT screening for individuals between ages 50 and 75. However, the optimal strategy to adjust to limited colonoscopy capacity is unclear.

There are several established ways to limit colonoscopy demand. One way is to screen individuals less frequently by starting screening at older ages, stopping at younger ages, or by increasing the screening interval. Use of a more specific test or hemoglobin cutoff level is another strategy to limit colonoscopy demand. Finally, reduction of colonoscopy demand can be achieved by more selective referral of individuals to surveillance colonoscopy after adenoma removal. We assessed which are the most clinically effective and cost-effective FOBT screening alternatives under different colonoscopy capacity levels with the validated MISCAN-Colon micro-simulation model, using attendance rates, costs, positivity and detection rates of gFOBT and FIT at varying hemoglobin cutoff levels from two implementation trials in the Netherlands.[5,6]

Methods

MISCAN-Colon

The MISCAN-Colon micro-simulation model and the data sources that inform the quantification of the model are described in detail in previous publications[15,16] and in a standardized model profile.[17] In brief, the model simulates the relevant biographies of a large population of individuals from birth to death (n = 1 000 000 individuals per simulated strategy), first without screening and subsequently with the changes that would occur under the implementation of a screening program. In every individual one or more adenomas may arise and some of them may develop into cancer. Adenomas can progress from small (1-5 mm) to medium (6-9 mm) to large (10+ mm). The majority of adenomas are assumed to be non-progressive and will never develop into cancer. The progressive adenomas have the ability to become cancer, but not all of them will because the individual may die of causes other than CRC. The adenomas that become malignant transform into stage I cancers and may successively progress to stage II, III and IV until they are diagnosed at one of these stages. After diagnosis, the patient will or not die of CRC, depending on the stage specific survival, and again, may die of other causes. The same life history is simulated by the model for the situation with screening. An individual with an adenoma or cancer has a chance of having it detected during a screening round depending on the sensitivity of that test for that lesion. After a person tests positive, he/she is referred for colonoscopy for removal of adenomas and diagnosis of cancers. In this way, CRC incidence or CRC death can be prevented. For the situations with and without screening, the life-years lived are aggregated over the total simulated population. The life-years gained by screening are calculated as the difference between these totals.

The model reproduced the Dutch population with age distribution during the year 2005 (Statistics Netherlands, www.cbs.nl), with the cancer incidence as observed in the Netherlands from 1999-2003 (Comprehensive Cancer Centre (CCC), www.ikcnet.nl). Survival after clinical diagnosis of a cancer was on the basis of relative survival data from 1985-2004 from the South of the Netherlands,[18] since national data were not available. The survival for individuals aged 75 or older was adjusted to fit the observed age-increasing mortality/incidence ratio.

The validity of the model has successfully been tested on the results of large screening studies, such as the randomized FOBT trials in Minnesota, Funen and Nottingham,[19] and the CoCap sigmoidoscopy study in the United States.[15] Also, the model was validated with surveillance data from the National Polyp Study in the United States.[20] Additionally, when accounting for risk factor trends, screening practice and chemotherapy

treatment in the United States,[21] the model was able to reproduce observed incidence and mortality trends.

Test characteristics

When the MISCAN-Colon model was calibrated using three FOBT trials,[19] the modeled sensitivity of gFOBT for CRC increased with a shorter time until the cancer would have been diagnosed by symptoms *vs* screening (Table 4-1). Other test characteristics were fitted to the positivity and detection rates as observed in the first screening round of the Dutch trials[4-7] (Tables 4-1 and 4-2). Because FIT also tests for blood in the feces, we assumed that the sensitivity of FIT for CRC depended on the time until diagnosis, similar to that of gFOBT. We assessed FIT at varying hemoglobin cutoff levels for referral to colonoscopy: 50, 75, 100, 150 and 200 ng hemoglobin/ml. Colonoscopy sensitivity was assumed to be 75% for adenomas 1-5 mm, 85% for adenomas 6-9 mm, and 95% for both adenomas 10 mm or more and CRC.[22]

Screening, surveillance strategies, and attendance assumptions

We simulated screening in the Dutch population during a period of 30 years starting in 2005, including 48 screening strategies per test (gFOBT or FIT at 50,75, 100, 150, 200 ng hemoglobin per ml). The 48 combinations were obtained by varying the age to start screening (45, 50, 55, and 60 years), the age to stop screening (70, 75, and 80 years), and the screening interval (1, 1.5, 2 and 3 years).

After a positive FOBT, a diagnostic colonoscopy was offered. If no adenomas or CRC were found at the time of the colonoscopy, an individual was offered repeat FOBT screening after 10 years. If one or more adenomas were found during the colonoscopy, the adenomas were removed by polypectomy. We simulated two surveillance policies for individuals who had adenomas removed: 1) Current Dutch guidelines,[23] which dictate that the next colonoscopy is offered after 6 years when one or two adenomas are found and after 3 years when three or more adenomas are found, and 2) less intensive surveillance in which individuals with one or two adenomas of no more than 10 mm in diameter are returned to screening and offered FOBT after 10 years (same strategy as for individuals with a negative colonoscopy after a positive FOBT). Other individuals were referred to colonoscopy on the basis of current surveillance guidelines. We assumed that surveillance stopped at the age of 80 years, the oldest age at which screening is stopped in the considered strategies.

Attendance rates for gFOBT, FIT and diagnostic colonoscopy were based on the Dutch trials (50%, 60%, and 85%, respectively).[5,7] Attendance to surveillance colonoscopies was assumed to be 80%.[24] Based on a gFOBT trial, we also assumed that 10% of

*Table 4-1. Specificity and sensitivity of guaiac fecal occult blood test (gFOBT) and fecal immunochemical test (FIT) at various hemoglobin cutoff levels to detect adenomas and colorectal cancer (CRC)**

		Sensitivity per lesion, %†				
Test	Specificity per person, %	Adenoma ≤5 mm	Adenoma 6–9 mm	Adenoma ≥10 mm	CRC, all stages before diagnosis in the absence of screening	CRC, stages at diagnosis in the absence of screening
gFOBT	98.9	0	1.3	6.5	18.2	50.8
FIT 200 ng hemoglobin per mL	98.7	0	2.0	10.6	46.0	80.0
FIT 150 ng hemoglobin per mL	98.3	0	2.3	12.2	47.0	81.0
FIT 100 ng hemoglobin per mL	97.8	0	4.0	13.0	51.0	83.0
FIT 75 ng hemoglobin per mL	97.0	0	4.1	15.2	56.0	85.5
FIT 50 ng hemoglobin per mL	95.8	0	8.4	16.7	61.0	88.0

* The sensitivity for CRC is assumed to be higher in the stage at diagnosis in the absence of screening than in earlier stages. The average duration of each preclinical CRC stage is 2.5, 2.5, 3.7, and 1.5 years in stage I, II, III, and IV, respectively. The total duration accumulates with the stage progression and corresponds with the duration of a low or high sensitivity (eg, sensitivity is low during on average 5 years for a CRC diagnosed in stage III without screening).
† Excluding the probability that an adenoma or cancer is found because of a lack of specificity.

Table 4-2. Modeled and observed positivity rates and detection rates per 100 screened individuals (highest grade finding per individual) for guaiac fecal occult blood test (gFOBT) and fecal immunochemical test (FIT) at various hemoglobin cutoff levels in the first screening round.

	Positivity rate, %		Detection rate of no adenomas or CRC, %		Detection rate of non-advanced adenomas, %		Detection rate of advanced adenomas*, %		Detection rate of colorectal cancer, %	
Test	Modeled	Observed	Modeled	Observed	Modeled	Observed	Modeled	Observed	Modeled	Observed
gFOBT	2.5	2.5	98.5	98.5	0.35	0.33	0.98	0.97	0.20	0.24
FIT 200 ng hemoglobin per mL	3.7	3.7	97.6	97.6	0.48	0.48	1.54	1.54	0.39	0.39
FIT 150 ng hemoglobin per mL	4.4	4.4	97.2	97.2	0.59	0.58	1.78	1.82	0.40	0.40
FIT 100 ng hemoglobin per mL	5.3	5.3	96.8	96.8	0.83	0.80	1.98	2.01	0.42	0.42
FIT 75 ng hemoglobin per mL	6.4	6.4	96.3	96.3	0.99	1.02	2.30	2.27	0.45	0.45
FIT 50 ng hemoglobin per mL	8.4	8.4	95.2	95.3	1.57	1.54	2.73	2.71	0.48	0.48

* Advanced adenoma was defined as an adenoma of 10 mm or larger in diameter, or a histology showing either at least a 25% villous component or high-grade dysplasia in the trials. In the model, adenomas are classified by size only, and advanced adenomas were all assumed to be 10 mm or larger in diameter.

the individuals never attended FIT screening[25] and that never attendees had a higher risk for CRC than the general population (RR=1.15).[1] Of the individuals who did attend in a certain screening round, 80% attended again in the subsequent screening round,[26] but this imbalance was corrected by attendance of individuals who did not attend the previous screening round, so that the overall attendance rates stayed at 50% and 60% for gFOBT and FIT respectively in each screening round.

Costs

We included screening and treatment costs in the analysis (Table 4-3). Organizational costs for FOBT screening were based on current expenses in the Dutch cervical cancer screen program and were adjusted for differences with FOBT screening. Cost assumptions for the test kits were based on prices of the manufacturer. Costs for analysis of the tests consisted of costs for material and personnel needed during the process of registration, analysis and authorization of returned tests. Colonoscopy costs were based on a 6-month-long study at the Erasmus MC (Rotterdam, the Netherlands). Additional costs for polypectomy were based on additional time, polypectomy materials needed for the procedure, and costs for pathology. Complications during or after colonoscopy can occur, such as perforations or bleeding. Costs for complications after colonoscopy were based on DBC-rates (Diagnosis Treatment Combination), derived from the Dutch Health Care Authority (http://ctg.bit-ic.nl/Nzatarieven/top.do).

Costs of CRC were divided into three clinically relevant phases of care: initial treatment, continuous care and terminal care. Initial treatment costs were based on DBC-rates, except for Oxaliplatin. The costs for Oxaliplatin were derived from the Dutch Health Care Insurance Board (www.medicijnkosten.nl). We assumed that during the continuous care phase, individuals followed the Dutch guidelines (www.oncoline.nl) and costs for periodic control were based on DBC-rates. Terminal care costs for patients who ultimately died of CRC were based on a last year of life analysis and were estimated at €19,700.[27] We assumed that terminal care costs increase with stage, as was previously observed for patients in the United States.[28,29] Dutch terminal care costs for individuals who died of CRC were approximately 40% of the US costs. We assumed that terminal care costs of CRC patients who died of other causes were also 40% of the US costs.

Limited colonoscopy capacity

Colonoscopy capacity was defined as the number of colonoscopies available per year for CRC screening and diagnosis per 1,000 individuals aged between 45 and 80 years in the year 2005. The number of colonoscopies included diagnostic colonoscopies after a posi-

*Table 4-3. Model assumptions of the base case and sensitivity analyses**

	Assumptions	
Variable	**Base case analysis**	**Sensitivity analysis**
Attendance	FIT = 60% gFOBT = 50% Diagnostic colonoscopy = 85% Surveillance colonoscopy = 80%	FOBT = 100%; Colonoscopy = 100%
Quality of life loss		
Colonoscopy	NA	1 d lost per colonoscopy;
CRC from diagnosis onwards† (1-utility‡)	NA	Initial treatment[42]: Stage I = 0.26 during 1 year; Stage II = 0.3 during 1 year; Stage III = 0.4 during 1 year; Stage IV = 0.75 during 1 year; Continuous care[43] = 0.15 in years in between initial and terminal phase; Terminal care death by CRC = 0.75 in last year before dying of CRC; Terminal care death by other cause = 0.35 in the last year before dying of other causes.
Correlation FOBT results	NA	74% of the large adenomas (>9 mm) that are not detected will not be detected in the next screening round[30]
Fatal complications after colonoscopy	One fatal complication per 10,000 colonoscopies	Low = 0 fatal complications; high = 1 fatal complication per 1,000 colonoscopies with polypectomy or 1 fatal complication per 10,000 colonoscopies without polypectomy
Costs per invitation (organizational costs and test kit)		
gFOBT	€14.05	Low = 50%; high = 200%
FIT	€14.85	
Costs per attendee (personnel and material costs for analysis)		
gFOBT	€1.90	These costs were varied to 50% and 200% in parallel with the costs per invitation.
FIT	€4.37	
Colonoscopy costs		
Without polypectomy	€303	Low = 50%; high = 200%
With polypectomy	€393	
Costs associated with complications after colonoscopy†	€1,250	Low = 50%; high = 200%
Treatment costs by stage§		Low = 50%, high = 200%
Stage I		
Initial treatment	€12,500	Treatment costs of stage I, II, III, and IV were varied at the same time
Continuous care	€340	
Terminal care, death from CRC	€17,500	
Terminal care, death from other cause	€4,400	

Table 4-3. Continued

	Assumptions	
Variable	**Base case analysis**	**Sensitivity analysis**
Stage II		
Initial treatment	€17,000	Treatment costs of stage I, II, III, and IV were varied at the same time
Continuous care	€340	
Terminal care, death from CRC	€17,500	
Terminal care, death from other cause	€4,000	
Stage III		
Initial treatment	€21,000	Treatment costs of stage I, II, III, and IV were varied at the same time
Continuous care	€340	
Terminal care, death from CRC	€18,500	
Terminal care, death from other cause	€5,200	
Stage IV		
Initial treatment	€25,000	Treatment costs of stage I, II, III, and IV were varied at the same time
Continuous care	€340	
Terminal care, death from CRC	€25,000	
Terminal care, death from other cause	€14,000	

* CRC = colorectal cancer; FIT = fecal immunochemical test; FOBT = fecal occult blood test; NA = Not Applicable.
† The assumed complication rate is 2.4 complications per 1000 colonoscopies, and 0.1 complications per 1000 colonoscopies is assumed to have a lethal complication.
‡ 1-utility describes the loss in quality of life because of the health states listed.
§ CRC treatment was divided into three clinically relevant phases—initial, continuous, and terminal care. The initial phase was defined as treatment administered during the first 12 months following diagnosis, the terminal phase was defined as the final 12 months of life, and the continuous phase was defined as all months between the initial phase and the beginning of the terminal phase. For patients surviving less than 24 months after diagnosis, the final 12 months of observation and costs of care were then allocated first to the last year of life phase because the content of care for patients with short survival is more similar to the last year of life phase than the initial phase. The remainder of months of observation and costs were allocated to the initial phase, with no contribution to the continuing phase.

tive FOBT, surveillance colonoscopies, and colonoscopies that preceded the diagnosis of a cancer outside the screening program. The cost-effectiveness analysis over 30 years of screening after introduction of a screening program was first done under the assumption of an unlimited colonoscopy capacity and repeated for different colonoscopy capacity levels of on average 5, 10, 20, and 40 colonoscopies per year per 1,000 individuals aged 45-80 years. The analyses at different capacity levels together were the base case.

Cost-effectiveness analysis

We used MISCAN-Colon microsimulation model to estimate costs and number of life-years gained for all screening strategies and cutoff levels compared to the situation without screening. Costs and life-years gained were discounted by 3% annually. Strate-

gies that were more costly and less effective than one or more other strategies were ruled out by simple dominance. Strategies that were more costly and less effective than a mix of other strategies were ruled out by extended dominance. The remaining strategies are known as "efficient". On a plot of costs *vs* life-years gained, the line that connects the efficient strategies is called the efficient frontier, and all dominated strategies lie below this line. The incremental cost-effectiveness ratio (ICER) of an efficient strategy was determined by comparing the additional clinical benefit and costs with those of the next less costly and less effective efficient strategy.

Sensitivity analysis

In addition to the base case analysis, we performed 13 sensitivity analyses on eight parameters (Table 4-3). Attendance rates were increased to 100% for FOBT and colonoscopy, representing the schedules for individuals who followed the recommendations. We adjusted for reduced quality of life because of screening as well as CRC treatment. Correlated FOBT results were assumed to account for the possibility that lesions that were difficult to detect in a screening round may be difficult to detect in the next round as well. We used the results of a population based screening program in Italy to estimate the correlation between false-negative FIT results for cancers and advanced adenomas in subsequent screening rounds.[30] We evaluated low and high values for the number of fatal complications, and for costs of FOBT, colonoscopy, complications, and treatment. We decided not to perform a probabilistic sensitivity analysis after having weighed the limited added value against the computational effort required (see Discussion).

RESULTS

Cost-effectiveness analysis

Efficient strategies with an ICER below €20.000 per life-year gained were investigated for an unlimited colonoscopy capacity and for a limited colonoscopy capacity of 40, 20, 10 and 5 colonoscopies per year per 1000 45- to 80-year-olds during the year 2005 (Figure 4-1 and Table 4-4). For an unlimited capacity, it was most beneficial to screen intensively with the lowest FIT hemoglobin cutoff level for referral to colonoscopy set at 50 ng/ml for those aged 45 to 80 years with an annual screening interval and offering colonoscopy surveillance to all individuals with adenomas. The colonoscopy demand with this strategy was 49 per 1,000 individuals. To optimally adapt screening when capacity was limited to 40 colonoscopies per 1,000 individuals, individuals with a FIT hemoglobin measurement between 50 and 75 ng/ml were no longer referred to

*Table 4-4. Most effective fecal immunochemical test (FIT) strategy with an incremental cost-effectiveness ratio (ICER) below €20 000 per life-year gained per colonoscopy restriction**

Maximum no. of colonoscopies†	FIT hemoglobin cutoff, ng/mL	Surveillance strategy*	Beginning-end age (No. of years in between), y	Screening interval, y	No. of screening rounds	Costs†	No. of life-years gained†	ICER	Average number of colonoscopies per year (undiscounted)
Unlimited	50	GS	45–80 (35)	1	36	€493	109	€16,200	49
40	75	GS	50–80 (30)	1	31	€415	99	€17,700	36
20	200	LS	50–75 (25)	1	26	€360	78	€17,900	20
10	200	LS	60–80 (20)	2	11	€175	48	€8,600	10
5	200	LS	60–69 (9)	3	4	€73	24	€3,000	5

* GS = surveillance after polypectomy following established guidelines; LS = less intensive surveillance with no surveillance for individuals with one or two adenomas <10 mm.
† Maximum number of colonoscopies, costs, and life-years gained are per 1000 individuals aged 45–80 years during the year 2005. The number of colonoscopies is undiscounted, although the costs and life-years gained are discounted by 3% annually.

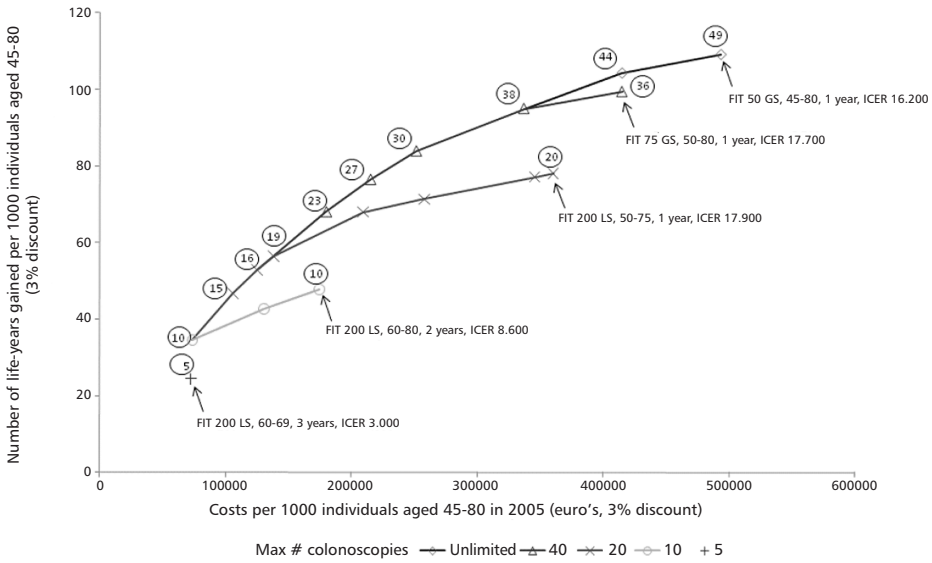

*Figure 4-1. Efficient strategies per colonoscopy capacity restriction. The strategies vary by age to begin and end screening, screening interval, screening test, and surveillance strategy. Screening tests included guaiac fecal occult blood test or fecal immunochemical testing (FIT) with hemoglobin cutoff levels of 50, 75, 100, 150, or 200 ng/mL. The number of life-years gained and costs of 30 years of screening were calculated per 1000 individuals (age 45–80 years) in 2005 and discounted by 3% annually. Colonoscopy capacity was unlimited (**diamonds**) or set to a maximum of 40 (**triangles**), 20 (**times symbol**), 10 (**circles**), or 5 (**plus**) colonoscopies per 1000 individuals. For every colonoscopy capacity level, a **line** connects the corresponding efficient strategies. The most effective strategies are given, and list the FIT hemoglobin cutoff level (ng/mL) with either less intensive surveillance with no surveillance for individuals with one or two adenomas smaller than 10 mm in diameter (LS) or surveillance after polypectomy following guidelines (GS), the beginning and ending screen age, the screening interval, and the incremental cost-effectiveness ratio (ICER, in euros). For each strategy, the number of colonoscopies needed is displayed by a **circled number**.*

colonoscopy and individuals between ages 45 and 50 years were no longer invited. This decreased the demand to 36 colonoscopies per 1,000 individuals. If capacity was limited to 20 per 1,000 individuals, the next step was to further increase the FIT hemoglobin cutoff to 200 ng/ml and to stop screening 5 years earlier at age 75. Also surveillance colonoscopies in individuals with only one or two non-advanced adenomas were cancelled.

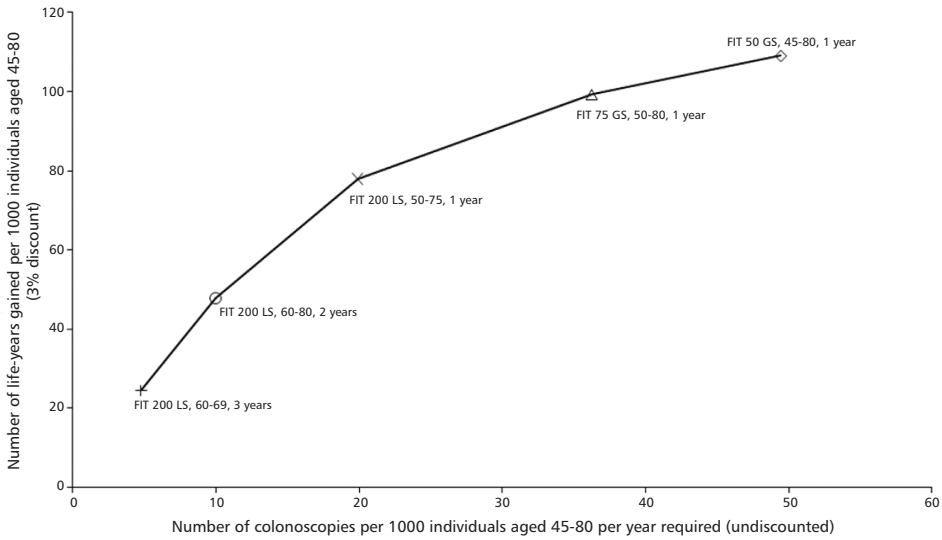

*Figure 4-2. The maximum number of life-years gained by colonoscopy demand with an incremental cost-effectiveness ratio below €20 000 per life-year gained. The efficient frontier (line) connecting efficient strategies to adapt fecal immunochemical testing (FIT) by altering the hemoglobin cutoff levels (200, 75, and 50 ng/mL) and the surveillance strategy, the beginning and ending screen age, the screening interval, and the incremental cost-effectiveness ratio (euros) is shown. The surveillance strategy was either less intensive surveillance with no surveillance for individuals with one or two adenomas smaller than 10 mm in diameter (LS) or surveillance after polypectomy following guidelines (GS). Data is shown for when colonoscopy capacity was unlimited (**diamonds**) or set to a maximum of 40 (**triangles**), 20 (**times symbol**), 10 (**circles**), or 5 (**plus**) colonoscopies per 1000 individuals. The number of life-years gained per 1000 individuals aged 45–80 is discounted by 3%, whereas the number of colonoscopies per year are undiscounted.*

If colonoscopy demand had to decrease even further, it became efficient to greatly reduce the number of screening rounds by first narrowing the age range to 60-80 years and lengthening the screening interval to 2 years (11 rounds) to reach a demand of 10 colonoscopies per 1,000 individuals, and then to narrow the age range to 60-69 every 3 years (4 rounds) for a final capacity of 5 colonoscopies per 1,000 individuals. Efficient screening with limited colonoscopy capacity had fewer health benefits and was less cost-effective compared with screening with a higher colonoscopy capacity: with more colonoscopies, there are strategies with the same costs but more life years gained that had an ICER below €20,000 per life-year gained (Figure 4-1).

Screening with gFOBT never became a cost-effective alternative. The gFOBT strategy with the lowest colonoscopy demand (gFOBT, age 60-69 years, screened every 3 years, with less intensive surveillance) required 3 colonoscopies per 1000 individuals. However, setting a FIT hemoglobin cutoff level of 200 ng/ml for 63- and 66-year-olds with less intensive surveillance required the same number of colonoscopies at lower costs (€37,000 *vs* €53,000 per 1,000 individuals for FIT and gFOBT, respectively) and resulted in more life-years gained (14 *vs* 12 life-years gained per 1,000 individuals for FIT and gFOBT, respectively) (data not shown).

The relationship between the life-years gained and the colonoscopy demand was also investigated (Figure 4-2 and Table 4-4). At the lower end, doubling the number of colonoscopies required from 5 to 10 colonoscopies per 1,000 individuals doubled the number of life-years gained from 24 to 48. At the high end, increasing colonoscopy demand by more than 25% increases the life-years gained by 10%.

Sensitivity analysis

The most effective strategies with an ICER below €20,000 per life-year gained for the base case and the sensitivity analyses per level of colonoscopy capacity restriction were investigated (Table 4-5). Halving the costs for FOBT, colonoscopy or complications, or doubling the costs for complications found the most beneficial strategies were the same as the base case at all capacity levels (Table 4-5). In the other sensitivity analyses, at least at one capacity level there was a change in which strategies were most beneficial because the base case strategy became more costly than €20,000 per life-year gained, or because the base case strategy was now dominated by alternative strategies. None of the cost and the fatal complication rate variables were of influence if capacity was 10 or 5 colonoscopies per 1,000 individuals aged 45-80 years.

In all sensitivity analyses, the FIT hemoglobin cutoff value for referral to colonoscopy increased with a decreasing colonoscopy capacity, except for the analysis with an assumed 100% attendance (Table 4-5). The optimal hemoglobin cutoff value increased more slowly compared with that of the base case when we used quality adjusted life-years and when FOBT costs were doubled. Under these conditions, there was an extra penalty on quality of life or costs, for primary screening, which was in favor of less frequent screening with a lower cutoff relative to more frequent screening with a higher cutoff. When we assumed a correlation between repeated false negative FOBT results for individuals with large adenomas, it was only cost-effective to offer less surveillance to individuals with adenomas less than 10 mm in diameter for less than 5 colonoscopies per 1,000 individuals (Table 4-5). Under this assumption, FOBT missed large adenomas more often and offering individuals in whom any other adenoma had been detected

*Table 4-5. Sensitivity analyses of the most effective strategies with an incremental cost-effectiveness ratio below €20 000 per life-year gained per colonoscopy restriction**

		Assumptions for sensitivity analyses												
Maximum No. of colonoscopies	Base case	Attendance 100%	Quality-adjusted life-years	Correlated FOBT results	Fatal complications (low)	Fatal complications (high)	1/2 FOBT costs	2 × FOBT costs	1/2 Colonoscopy costs	2 × Colonoscopy costs	1/2 complication costs	2 × complication costs	1/2 tx costs	2 × tx costs
Unlimited														
FIT	FIT 50	B	B	FIT 50	B	FIT 50	B	FIT 50	B	FIT 50	B	B	B	B
Surveillance	GS			GS†		GS†		GS†		GS†				
Age group, y	45–80			50–80		50–80		50–80		50–80				
Frequency, y	1			1		1		1		1				
40														
FIT	FIT 75	FIT 100	FIT 50	FIT 50	B	B	B	FIT 50	B	B	B	B	B	FIT 50
Surveillance	GS	GS	GS†	GS				GS†						GS†
Age group, y	50–80	45–79.5	55–80	50–75				55–80						55–80
Frequency, y	1	1.5	1	1				1						1
20														
FIT	FIT 200	FIT 200	FIT 75	FIT 200	FIT 200	B	B	FIT 75	B	FIT 200	B	B	FIT 200	B
Surveillance	LS	GS	LS†	GS	LS†			GS†		LS†			LS†	
Age group, y	50–75	55–79	55–74.5	50–80	55–80			55–79		55–80			55–80	
Frequency, y	1	2	1.5	1	1			2		1			1	
10														
FIT	FIT 200	FIT 150	FIT 200	FIT 200	B	B	B	B	B	B	B	B	B	B
Surveillance	LS	LS	GS	GS										
Age group, y	60–80	60–69	55–74	55–75										
Frequency, y	2	3	3	2										
5														
FIT	FIT 200	N	B	B	B	B	B	B	B	B	B	B	B	B
Surveillance	LS													
Age group, y	60–69													
Frequency, y	3													

* B = the same strategy was used as was used in the base case analysis; FIT = fecal immunochemical test; FOBT = fecal occult blood test; GS = surveillance after polypectomy following guidelines; LS = less intensive surveillance with no surveillance for individuals with one or two adenomas <10 mm; N = no strategies met the requirement of fewer than five colonoscopies per year per 1000 individuals aged 45–80 years during the year 2005, tx = treatment. FIT 200, FIT 150, FIT 100, FIT 75, and FIT 50 indicate a FIT hemoglobin cutoff of 200, 150, 100, 75, or 50 ng hemoglobin per mL.

† These strategies replaced the base case strategies because the base case strategies were on the efficient frontier (Figure 4-1), but with an incremental cost-effectiveness ratio of more than €20 000 per life-year gained. All other strategies replaced the base case strategies because the base case strategies were not on the efficient frontier.

was therefore more important. Screening intervals were longer when we assumed 100% attendance and when we adjusted for quality of life. If 100% attendance was reached, the longer screening intervals compensated for the fact that individuals were participating in all screening rounds.

Discussion

There are several ways to adjust an FOBT screening program to a limited colonoscopy capacity. After assessing the most effective and cost-effective FOBT screening alternatives under different colonoscopy capacity levels, we found that a FIT hemoglobin cutoff level of 50 ng/ml for referral to colonoscopy was most effective at all cost levels when colonoscopy capacity is unlimited, and higher cutoff levels are most effective when there is a limited colonoscopy capacity. Excluding individuals with one or two adenomas less than 10 mm in diameter from surveillance colonoscopy and reducing the number of screening rounds are next most effective strategies to reduce the colonoscopy demand. For all levels of colonoscopy capacity, FIT screening was more effective clinically and in terms of cost compared with gFOBT screening. The same patterns were found in the sensitivity analyses.

Increasing the FIT hemoglobin cutoff level – which was efficient when there was a decrease in colonoscopy capacity – resulted in higher-risk individuals being referred to colonoscopy. The health benefit per colonoscopy in terms of life-years gained as well as cost savings from treatment is greater in higher-risk individuals; so these individuals should be given the highest priority to receive a colonoscopy in a situation of limited capacity.

We presented the average number of colonoscopies over 30 years of screening. The number of colonoscopies varied over time because of an increasing number of individuals in the screen-eligible population, an increasing number of individuals in surveillance, and a lower positivity rate in subsequent screening rounds compared with the first screening round. Others reports previously estimated the annual number of colonoscopies for gFOBT screening as ranging from three to eight colonoscopies per 1,000 individuals aged 50-74[31-34] for biennial screening, depending on the age range considered (smallest 60-69 years and widest 50-74 years of age). Our estimates of 5.7 and 10.8 colonoscopies per 1,000 individuals aged 50-74 (corresponding to 4.4 and 8.1 colonoscopies per 1,000 individuals aged 45-80 years) for biennial screening between ages 60 and 69 and between 50 and 74 , respectively, are somewhat higher, possibly because of the longer screening horizon (30 compared to 15 years[33] and 10 years[32]), or because of differences in surveillance strategies.[34]

Our study is not without limitations. We performed one-way sensitivity analyses to evaluate the impact of other assumptions for some of the parameters. We did not perform a probabilistic sensitivity analysis. Given the large number of strategies that has to be evaluated for each draw, such an analysis would require a huge computational effort. We believe that simulating all these varying strategies is one of the strengths of this analysis because we were primarily interested in the comparison of a different cutoff level with different screening frequencies and ages, and different surveillance strategies. Regardless, data on the probability distributions of most of the parameter values are lacking, which makes the interpretation of a probabilistic sensitivity analysis difficult and the outcome of limited added value. One of the most uncertain assumptions of the model is that all CRCs arise from adenoma precursors. For FOBT screening, this assumption will have limited impact because FOBT has a low sensitivity for adenomas, and the assumption of non-bleeding and therefore for FOBT undetectable adenomas was evaluated in the sensitivity analysis by assuming correlation between false negative results.

There is uncertainty about the effects of changing the surveillance policy regarding small adenomas. The validity of our model was tested on the National Polyp Study,[20] where individuals received several surveillance colonoscopies. A substantial proportion of the individuals only had one or two small adenomas. Nonetheless, the evidence on the effectiveness of surveillance colonoscopy, especially in individuals with one or two small adenomas (<10mm in diameter), is limited. Therefore, we also looked at our results when not varying the surveillance strategy. This had no impact on which FIT hemoglobin cutoff level was most beneficial and still cost-effective at the various colonoscopy capacity levels. Only for the lowest level of colonoscopy capacity (five colonoscopies per 1000 individuals), with surveillance according to guidelines (also surveillance in individuals with small adenomas), there were no FIT strategies with fewer than five colonoscopies per 1000 individuals. We considered strategies with an ICER value less than 20,000 euro per life-year gained. This was hardly restrictive because only one of the efficient strategies for the base case had a higher ICER value (€53,000 per life-year gained). We did not include more intensive screening strategies (eg, age ranges wider than 45-80 years or screening intervals of <1 year) because data are not available to validate the model predictions.

Several other tests are currently being used for CRC screening. Hemoccult Sensa is a guaiac-based FOBT with a similar sensitivity as FIT; however, the lack of specificity is three times higher than that of FIT.[35] The test costs, laboratory requirements, and procedures for the two FOBTs are similar; however, the higher specificity makes FIT the preferred test. Flexible sigmoidoscopy has recently been shown to be highly effective in detecting distal lesions.[36] The results for proximal lesions, however, were disappointing.

Regardless, attendance to flexible sigmoidoscopy is substantially lower than that of FIT.[4] Flexible Sigmoidoscopy should therefore only be advocated in combination with FIT. Offering all individuals colonoscopy for primary CRC screening when there is a limited colonoscopy capacity is not supported by our results that only individuals with an increased risk for adenomas and CRC shown by a high level of hemoglobin in their stool, should be selected to get colonoscopy.

Estimates of the current colonoscopy capacity differ between countries,[8,10,37-40] and even within countries.[37,39,40] How much of the available capacity can or is being used for screening is often unclear. Usually, introduction of a population-wide screening program requires expansion of the colonoscopy capacity. Because this takes time, a screening program needs to be introduced stepwise. Our results show that from a cost-effectiveness perspective, this can best be done by increasing the referral threshold for FIT. Besides cost-effectiveness, other aspects such as organizational aspects should be considered. Fortunately, starting with a higher cutoff level, and subsequently lowering it stepwise, is probably the easiest way to implement a screening program. Adding age groups by beginning screening earlier and stopping later in life is also feasible. However, changing surveillance guidelines may be confusing for individuals in whom adenomas have been detected under the old regime. Also, changing the screening interval could result in nonattendance, because people might think that they have erroneously received their screening invitation too early.

In some countries, organized FOBT screening has already started. Although a stepwise approach was used to implement these programs, no country considered using a FIT with a higher hemoglobin cutoff, the most (cost-)effective way according to our study. England and Finland started cautiously by using a gFOBT and inviting individuals biennially between ages 60 and 69. In England, the end age will be increased to 74 years during the year 2010. In some regions in Italy, individuals have been invited biennially between ages 50 and 70 with a FIT hemoglobin cutoff of 100 ng/mL. In Australia, FIT screening has started for individuals aged 55 and 65, with the intention to extend to biennial screening between ages 55 and 74.[41] Individuals are referred to colonoscopy if at least one of two tests determines that the amount of hemoglobin in the stool is more than 100 ng/ml. With the stepwise introduction of a screening program, it is important to also extend the colonoscopy capacity, to be able to screen more effectively in the future.

In conclusion, FIT is more cost-effective than gFOBT both with and without a limitation of the colonoscopy capacity but should be used in combination with a higher hemoglobin cutoff level for referral to colonoscopy when capacity is limited. It should be noted that FOBT screening can become considerably more effective if colonoscopy capacity is expanded. Efforts should therefore be undertaken to achieve an increased colonoscopy capacity.

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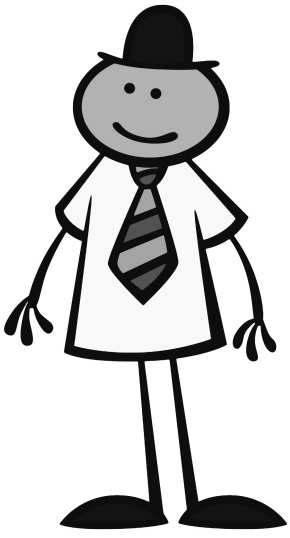
5

Diagnostic yield improves with collection of 2 samples in fecal immunochemical test screening without affecting attendance



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Abstract

Background & Aims: The fecal immunochemical test (FIT) is superior to the guaiac-based fecal occult blood test in detecting neoplasia. There are not much data on the optimal number of FITs to perform. We conducted a population-based trial to determine attendance and diagnostic yield of 1- and 2-sample FIT screening.

Methods: The study included two randomly selected groups of subjects aged 50–74 (1-sample FIT $n = 5{,}007$; 2-sample FIT $n = 3{,}197$). The 2-sample group was instructed to collect fecal samples on two consecutive days. Subjects were referred for colonoscopy when at least one sample tested positive (≥ 50 ng Hemoglobin/mL).

Results: Attendance was 61.5% in the 1-sample group (2,979 of 4,845; 95% confidence interval, 60.1-62.9%) and 61.3% in the 2-sample group (1,875 of 3,061; confidence interval, 59.6%–63.0%; $P = 0.84$). In the 1-sample group 8.1% tested positive, and in the 2-sample group 12.8% had at least one positive test outcome and 5.0% had two positive test outcomes ($P < 0.05$). When the mean from both test results in the 2-sample group was used, 10.1% had a positive test outcome ($P < 0.05$). The detection rates for advanced neoplasia were 3.1% in the 1-sample group, 4.1% in the 2-sample group with at least one positive test outcome, 2.5% when both test results were positive, and 3.7% among subjects with the mean from both test results being positive.

Conclusions: There is no difference in attendance for subjects offered 1- or 2-sample FIT screening. The results allow for the development of efficient FIT screening strategies that can be adapted for local colonoscopy capacities, rather than varying the cutoff value in a 1-sample strategy.

INTRODUCTION

Colorectal cancer (CRC) is a public health issue of high importance in Western countries because of its high incidence and mortality rates.[1] Screening of average-risk individuals can result in early detection of CRC and will therefore improve prognosis considerably.[2] Furthermore, most CRCs develop from benign adenomatous polyps and slowly progress over many years, providing a window of opportunity for detecting and removing precancerous polyps and earlystage cancers. Endoscopic removal of adenomas results in a lower than expected incidence of CRC, compared with reference populations.[3] Therefore, based on the characteristics of CRC, screening is of considerable value.

Colonoscopy is the most accurate test for detecting neoplasia and for the removal of adenomas. However, colonoscopy is associated with discomfort both related to the bowel preparation and the examination itself, and the procedure carries a small but distinct complication risk. Other limitations are the availability of qualified endoscopists and costs. For these reasons, other strategies have been proposed for nationwide CRC screening. There is considerable evidence that screening of asymptomatic average-risk individuals using guaiac-based fecal occult blood tests (gFOBT) can detect cancers at an early and curable stage, resulting in a reduction of CRC-related death of 15 to 33%.[4] Recently more evidence has become available that the fecal immunochemical test (FIT) is superior to gFOBT screening, both with respect to attendance and detection of advanced neoplasia.[5-10] Unfortunately, even bleeding advanced neoplasia may be missed with single-stool sampling because they bleed intermittently. Repeated testing probably increases test sensitivity, but it is unknown what effect this will have on attendance, colonoscopy demand, and diagnostic yield.

Therefore, the aim of our study was to compare the attendance and diagnostic yield of 1-sample versus 2-sample FIT screening in a range of different cutoff values.

METHODS

Study population

Demographic data of all individuals between the ages of 50 and 74 years in the southwest area of the Netherlands were obtained from municipal population registers. Two random samples were taken from the target population by a computer-generated algorithm (Tenalea, Amsterdam, the Netherlands). Selection occurred before invitation. Both groups were stratified for socio-economic status (SES) into group A (1-sample FIT screening, n = 5,007) or group B (2-sample FIT screening, n = 3,197) (Figure 5-1). Be-

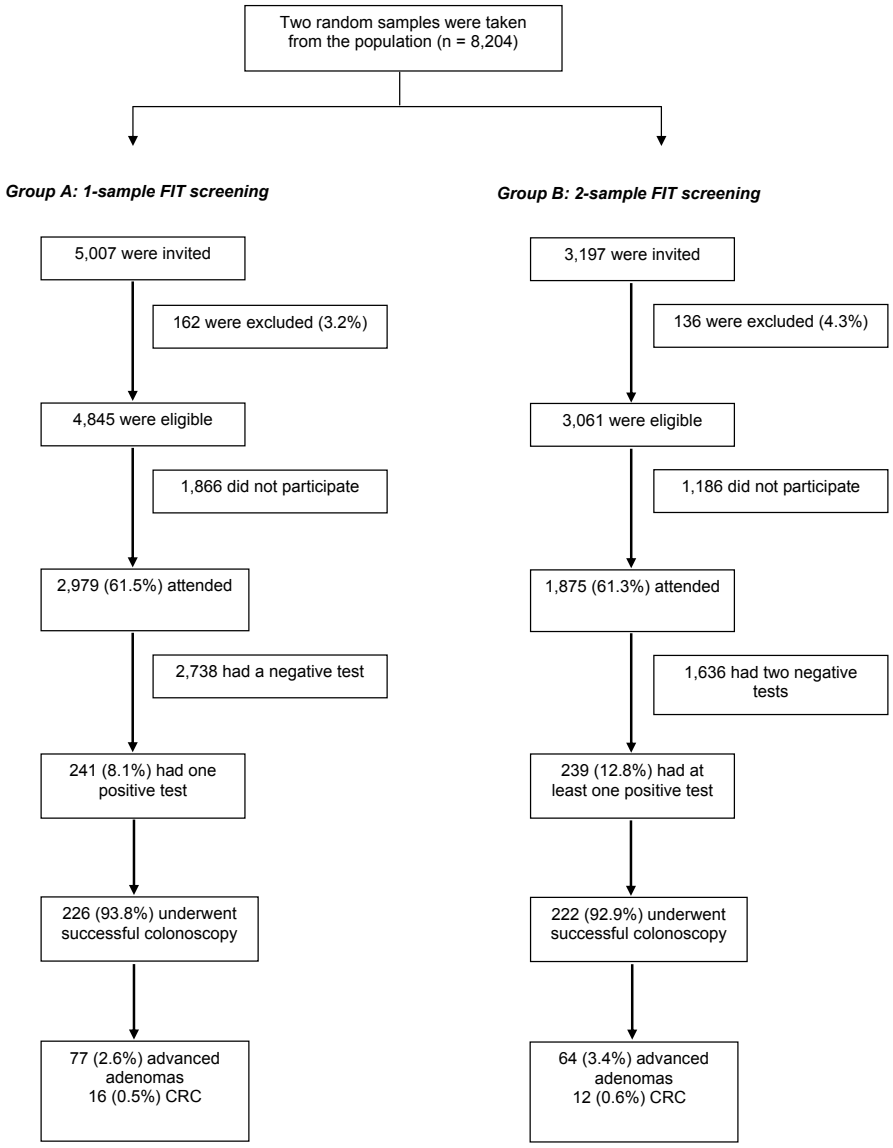

Figure 5-1. Trial profile.

cause there is no nationwide CRC screening program in the Netherlands, the population used for this trial was screening-naïve. The SES was based on the data from Statistics Netherlands (www.cbs.nl), providing average SES per postal code area, each representing small neighborhoods. Exclusion criteria were asked for on the informed consent form, which had to be filled in by the screened individual itself. Exclusion criteria were

a history of CRC; inflammatory bowel disease; a life expectancy of less than 5 years; a colonoscopy, sigmoidoscopy or double-contrast barium enema within the previous 3 years; and inability to give informed consent. Recruitment took place between November 2006 and December 2007 for the 1-sample FIT group, and between October 2008 and June 2009 for the 2-sample FIT group.

Group A: One-sample FIT screening

One FIT (OC-Sensor Micro, Eiken Chemical Co., Tokyo, Japan) was sent by mail to collect a single sample of one bowel movement. The test was considered positive when the hemoglobin (Hb) concentration in the FIT sample was 50 ng/mL or greater (1-sample FIT50). Details about the study design are described extensively elsewhere.[6]

Group B: Two-sample FIT screening

All subjects who were randomly selected for group B were sent two FITs. Explicit instructions were given to take one sample per FIT of two bowel movements on consecutive days, and to write down the sampling date on both test tubes. When both tests were performed on the same day, one additional FIT was sent to the screenee to make sure that two different stool samples were available from each individual. The test result was considered positive when the hemoglobin concentration in at least one FIT sample was 50 ng/mL or greater (2-sample FIT50).

Test result

In case of a positive test result, a colonoscopy was scheduled within four weeks. All colonoscopies were performed by experienced endoscopists. The maximum reach of the endoscope, adequacy of bowel preparation, and characteristics and location of all polyps were recorded. In accordance with the international classification, all removed polyps were evaluated by experienced gastrointestinal pathologists.[11]

Ethical approval

The study was approved by the Dutch Ministry of Health (PG/ZP 2.727.071 and PG/ZP 2.823.158). The study letters and information brochures were approved by the Institutional Review Board at Erasmus University Medical Centre (MEC-2005-264 and MEC-2008-029).

Power calculation

Assuming an attendance rate of 60% based on a previous CRC screening trial with FITs (one-sample) in the same region,[6] 3,200 invited individuals were needed to provide 80%

power for showing a 1% difference in diagnostic yield, with a standard error for the difference of 0.5%.

Statistical analysis

Differences in proportions between screening strategies were calculated using a χ^2 test. Differences in mean between screening strategies were calculated using a Student's *t*-test. All p-values were two-sided and considered significant if less than 0.05. The attendance rate was calculated by dividing the number of participants by all eligible subjects (defined as all invitees minus the excluded subjects). The positivity rate (PR) was defined as the proportion of participants having a positive test result. The detection rate (DR) was defined as the proportion of participants having advanced neoplasia. This was calculated as the number of screened individuals with an advanced neoplasia divided by all screened individuals with an analyzable screening test. Advanced neoplasia included CRC and advanced adenomas. An advanced adenoma was defined as an adenoma 10 mm or larger, or an adenoma with 25% or more villous component and/or high-grade dysplasia. When more than one lesion was present, the screenee was classified according to the most advanced lesion. Attendance, PR, positive predictive value (PPV), and DR were calculated and described as proportions with 95% confidence intervals (95% CI).

All test characteristics were calculated separately for both 1- and 2-sample FIT screening for cutoff levels varying from 50 to 200 ng Hb/mL in steps of 25. For the 2-sample FIT group, separate analyses were performed for at least one test being positive, both tests being positive, and the mean from both test results being positive.

For all different screening strategies, a graph was made in which the PR at the different cutoff values was plotted against the DR of advanced neoplasia per 100 screened individual. The line that connects the most efficient screening strategies is called the efficient frontier.

RESULTS

Attendance rate

Of the 5,007 subjects invited for 1-sample FIT screening, 162 individuals (3.2%) were excluded from analyses (142 subjects met one of the exclusion criteria, 13 had moved away, and 7 had died). In total, 61.5% (2,979 of 4,845; 95% CI: 60.1-62.9) attended 1-sample FIT screening. The FIT was analyzable in 2,975 individuals.

The 2-sample FIT group consisted of 3,197 invitees of whom 136 individuals (4.3%)

Table 5-1. Baseline characteristics of the two screening strategies.

	One-sample FIT screening	Two-sample FIT screening
Total number of invitees	5,007	3,197
Subjects included	4,845	3,061
Male sex, n (%)	2,508 (50)	1,593 (50)
Mean age, y (SD)	61 (7)	62 (7)
Socio-economic status, n (%)		
Low	2,011 (40)	1,277 (40)
Intermediate	975 (20)	638 (20)
High	2,021 (40)	1,282 (40)

SD, Standard deviation

were excluded from analyses (132 subjects met one of the exclusion criteria, 1 had moved away, and 3 had died). A total of 1,875 out of 3,061 eligible invitees (61.3%; CI: 59.6-63.0) responded to the 2-sample FIT invitation. The participation rate in both groups did not differ significantly (61.5% *vs* 61.3%, *P*-value 0.837; Figure 5-1). In total, 2 FIT samples were analyzable in 1,874 screenees.

Baseline characteristics of all randomly selected invitees did not differ between both screening strategies (Table 5-1).

Proportion of positive tests

At a cutoff value of 50 ng Hb/mL, the positivity rate (PR) of the 1-sample FIT group was 8.1% (95% CI: 7.2-9.1). At the same cutoff level, the PR of the 2-sample FIT group was 12.8% (95% CI: 11.4-14.4) when taking any positive test into account, 10.1% (95% CI: 8.8-11.5) when using the mean from both test results, and 5.0% (95% CI: 4.1-6.1) when taking two positive tests into account (Table 5-2). The PR of 1-sample FIT screening was statistically significantly lower than for the 2-sample FIT group with at least one positive test ($P < 0.001$), and with the mean from both test results ($P = 0.036$). In contrast, the PR of 1-sample FIT screening was statistically significantly higher than the 2-sample FIT group when requiring positive results for both tests ($P < 0.001$).

Follow-up evaluation

In the group of 1-sample FIT screening, 77 advanced adenomas and 16 CRCs were found (Figure 5-1). Overall, 81% of the detected advanced neoplasia was located in the distal colon (i.e. defined as descending colon, sigmoid and rectum). In the 2-sample FIT group, 64 advanced adenomas and 12 CRCs were found. In total, 83% of all detected

Table 5-2. Test characteristics of different FIT screening strategies (cutoff value, 50 ng Hb/mL).

	PR		PPV			NNScope		Detection rate				NNScreen	
								Advanced neoplasia		CRC			
Screening strategy	*n*	% (95%CI)	Advanced neoplasia % (95%CI)	CRC % (95%CI)	Advanced adenoma % (95%CI)	Advanced neoplasia, *n*	CRC *n*	*n*	% (95%CI)	*n*	% (95%CI)	Advanced neoplasia *n*	CRC *n*
One-sample FIT screening	241	8.1 (7.2-9.1)	41 (35-48)	7 (4-11)	34 (28-40)	2.4	14.1	93	3.1 (2.5-3.8)	16	0.5 (0.3-0.8)	32	186
Two-sample FIT (≥1 positive)	239	12.8 (11.4-14.4) *	34 (28-40)	5 (3-9)	29 (23-35)	2.9	18.5	76	4.1 (3.3-5.1)	12	0.6 (0.3-1.1)	25	156
Two-sample FIT (mean of both tests)	190	10.1 (8.8-11.5) *	39 (32-46)	7 (2-7)	32 (26-39)	2.6	14.8	69	3.7 (2.9-4.7)	12	0.6 (0.3-1.1)	27	156
Two-sample FIT (both positive)	94	5.0 (4.1-6.1) *	52 (42-62)	10 (5-18)	42 (32-53)	1.9	9.8	46	2.5 (1.9-3.3)	9	0.5 (0.3-1.0)	41	208

NNScope, number of colonoscopies that needs to be performed to find one screenee with advanced neoplasia; NNScreen, number of individuals that needs to be screened to find one individual with an advanced neoplasia; Advanced neoplasia, CRC and advanced adenoma; Advanced adenoma, adenoma ≥ 10 mm, or an adenoma ≥ 25% villous component and/or high-grade dysplasia.

* $P < 0.05$ compared with 1-sample FIT screening.

advanced neoplasia was located in the distal colon which was not significantly different compared with the 1-sample FIT group ($P = 0.707$).

Test characteristics

Between the 1-sample and 2-sample FIT groups, no statistically significant differences could be observed with respect to the PPV (Table 5-2; cutoff value 50 ng Hb/mL), although there was a trend for a higher PPV for the 2-sample FIT group with both positive tests compared with 1-sample FIT screening (52% *vs* 41%, respectively; $P = 0.075$).

Two-sample FIT screening with at least one positive test detected more advanced neoplasia than 1-sample FIT screening (1-sample FIT50: 3.1%; 95% CI 2.5-3.8%; 1-sample FIT200: 2.0%; 95% CI 1.6-2.6%; 2-sample FIT50: 4.1%; 95% CI 3.3-5.1%; 2-sample FIT200: 2.7%; 95% CI 2.1-3.5%). An increased DR for advanced neoplasia was also seen for the mean from both test results at any cutoff range. At a cutoff value of 50 ng Hb/mL, none of the observed differences in DR in the 2-sample FIT group compared to 1-sample FIT screening reached the level of statistical significance. However, a statistically significant difference in the DR was found between 2-sample FIT screening with at least one positive test compared with the 1-sample FIT group at cutoff levels of 75, 100, and 125 ng Hb/mL ($P = 0.017$, 0.032, and 0.039 respectively).

Positivity rate versus detection rate for advanced neoplasia

The PR of the different screening strategies was plotted at different cutoff values in the range of 50 to 200 ng Hb/mL against the DR for advanced neoplasia per 100 screened individuals (Figure 5-2). In terms of the number of colonoscopies per detected advanced neoplasia, the results can be subdivided in three parts along the PR-axis. At the low end, up to a PR of 3.2% the most efficient screening strategy is provided by 2-sample FIT screening with both FITs being positive at a cutoff value of 100 ng Hb/mL or greater. With lower cutoff levels, the PR of 2-sample FIT screening with both positive tests exceeds 3.2%, at which this strategy is outperformed by 1-sample FIT screening (Figure 5-2). Two-sample FIT screening with both positive tests generates a similar PR as gFOBT screening[7], however, with a higher DR for advanced neoplasia (Figure 5-2, lower left part of the graph). At the high end, at a PR of 6.2% the most efficient screening strategy is 2-sample FIT screening using either the mean from both test results, or at least one positive test (cutoff values of 50-175 ng Hb/mL). These strategies provide the highest DRs for advanced neoplasia, however, that is at the expense of high PRs and thus high colonoscopy demands (Figure 5-2). For the intermediate PR levels between 3.2% and 6.2%, the different screening strategies all lie very close to the efficient frontier.

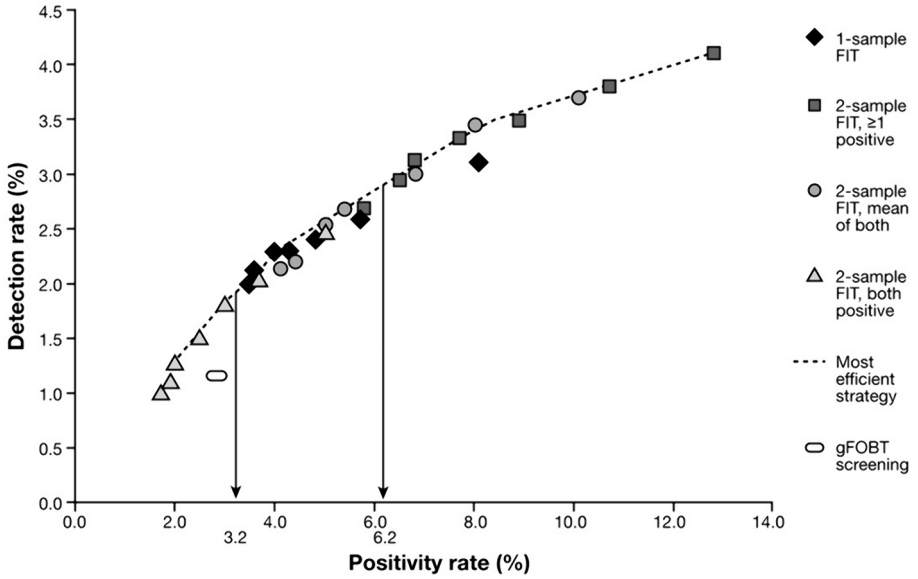

Figure 5-2. Positivity rate versus detection rate for advanced neoplasia (at different cutoff values). Per screening strategy, the data points represent the results at cutoff values in the range of 50-200 ng Hb/mL, increasing in steps of 25 ng. For each screening strategy, a higher cutoff level is associated with a lower detection rate, i.e. the data points at the left end represent the results at a cutoff value of 200 ng Hb/mL, where as the data point at the right end represents the results at a cutoff value of 50 ng Hb/mL. The arrows at positivity rates of 3.2 and 6.2% define zones in which either 1 or 2-sample FIT screening forms the most efficient strategy (see text).

Comparison of individual Fecal Immunochemical Tests in two-sample group

The laboratory test results generated for the 2-sample FIT group can be used to achieve more insight in the bleeding pattern of advanced adenomas (Table 5-3) and CRCs (Table 5-4), as well as to determine the additional value of a second test. At a cutoff value of 50 ng Hb/mL, in 27 of 64 screenees (42%) with an advanced adenoma, a discrepancy was seen between the first and last performed test. This means that in 42% of advanced adenoma cases, one of both tests was negative and the other one was positive (≥ 50 ng Hb/mL). For CRC, this discrepancy was 25% (3 of 12).

When we take the average of the first and the second tests in the 2-sample FIT group as reference, the PPV of a single test was 37%, with a DR for advanced neoplasia of 3.3%. This means that 31 individuals will need to perform one test (i.e. number needed to screen), and 3 screened individuals will need to be referred for colonoscopy to find one advanced neoplasia (i.e. number needed to scope). These results are quite compa-

Table 5-3. Comparison of first (vertical axis) vs last performed test (horizontal axis) in 64 screened individuals with an advanced adenoma in the 2-sample FIT group.

	0–49	50–74	75–99	100–124	125–149	150–174	175–199	200–224	225–249	>250	Totals
0–49	—	1	4	—	1	—	1	1	1	1	10
50–74	3	—	—	1	—	1	—	—	—	1	6
75–99	1	1	—	—	1	—	—	—	—	—	3
100–124	1	—	—	—	—	—	—	—	—	—	1
125–149	—	—	—	—	1	—	1	—	—	2	4
150–174	2	—	—	—	—	—	1	—	—	1	4
175–199	1	—	1	—	—	—	—	—	1	—	3
200–224	2	—	1	1	—	—	—	—	—	—	4
225–249	—	—	—	—	—	—	—	—	—	—	0
>250	7	3	1	4	—	1	—	—	—	13	29
Totals	17	5	7	6	3	2	3	1	2	18	64

NOTE. Hemoglobin concentration (ng Hb/mL) is shown.

Table 5-4. Comparison of first (vertical axis) vs last performed test (horizontal axis) in 12 screened individuals with a CRC in the 2-sample FIT group.

	0–49	50–74	75–99	100–124	125–149	150–174	175–199	200–224	225–249	>250	Totals
0–49	—	—	—	1	—	—	—	—	—	—	1
50–74	—	—	1	—	—	—	—	—	—	—	1
75–99	—	—	—	—	—	—	—	—	—	—	0
100–124	—	—	—	—	—	—	—	—	—	—	0
125–149	1	—	—	—	—	—	—	—	—	—	1
150–174	—	—	—	—	—	—	—	—	—	—	0
175–199	—	—	—	—	—	—	—	—	—	1	1
200–224	—	—	—	—	—	—	—	—	—	—	0
225–249	—	—	—	—	—	—	—	—	—	—	0
>250	1	—	—	—	1	—	—	—	—	6	8
Totals	2	0	1	1	1	0	0	0	0	7	12

NOTE. Hemoglobin concentration (ng Hb/mL) is shown.

rable with those of the 1-sample FIT group (Table 5-2). When the same data from the two tests were used to determine the added value of a second test, on average, 15 extra advanced neoplasms were found in 1,875 participants. The PPV and DR of an additional second FIT were 21% and 0.8% respectively. In other words, to find one extra advanced neoplasia by means of a second test, 125 additional individuals need to be screened and 5 additional colonoscopies need to be performed.

DISCUSSION

The efficacy of screening for CRC is determined by the attendance and diagnostic yield of a certain screening strategy. Several studies have shown that FIT screening outperforms the gFOBT on both parameters.[5-10] However, the optimal number of FITs to be used per screening round has not been elucidated. This trial showed no differences in attendance between 1-sample and 2-sample FIT screening. This observation is in accordance with an Italian study that also showed no difference in participation between 1-sample and 2-sample FIT screening (mean attendance rate 56%).[12] Therefore, the decision on the optimal number of FITs to be used for a nationwide screening program can be based on differences in test characteristics. Our results provide important new insights in strategies tailored to local situations, in particular colonoscopy capacity. In areas with limited access to colonoscopy the best way to get to a low PR is to use 2-sample FIT screening with referral for colonoscopy only when both tests are positive. This strategy yields more advanced neoplasia at the same or even lower colonoscopy demand compared with gFOBT screening, which guarantees optimal use of limited colonoscopy resources. The other extreme portrays a nationwide screening program in which colonoscopy capacity is not a limiting factor. In that setting, the strategy of 2-sample FIT screening with referral for colonoscopy in case of at least one positive test is associated with a significantly higher detection rate of advanced neoplasia than 1-sample FIT screening. For that reason, the optimal FIT screening strategy in regions with wider colonoscopy capacity is 2-sample FIT screening, whereby the positivity and detection rate can be tailored to meet colonoscopy availability and budgets by choice of the cutoff value (Figure 5-2). This starts by using 2-sample FIT screening with relatively high cutoff levels (100-200 ng Hb/mL). In case of even higher colonoscopy capacities, the most attractive option is to decrease the cutoff value of 2-sample FIT screening to less than 100 ng Hb/mL. In this range, the extra diagnostic yield per additional colonoscopy only slightly levels off (Figure 5-2). A full cost-effectiveness analysis should determine whether 2-sample FIT screening with such high PRs is still cost-effective. In between these two extremes, in the PR range of

3.2% to 6.2%, all screening strategies tested are very close to the efficient frontier (Figure 5-2). However, given the same attendance, a lower burden to the screened individuals and lower costs for one test, 1-sample FIT screening should be advised in those situations. Until now, limited data were available regarding the most optimal number of FITs to be used. Most data published used the highest Hb concentration of multiple samples (i.e. at least one test positive) and therefore valuable analyses about both positive tests or the mean of both FITs were missing.[13,14] The literature also lacks comparative trials of 1-sample versus 2-sample FIT screening with regard to attendance and diagnostic yield. Available studies compared the results of 2-sample or 3-sample FIT screening with either a gFOBT or an internal control group.[9,14-16] This latter means that 2- or 3-sample FIT screening was performed in a study in which analyses were done by considering the first performed test as representative for 1-sample FIT screening, and the combination of all test results as either 2-sample or 3-sample FIT screening. This approach provides some insight but does not allow any determination of differences in attendance rate and is confounded by the fact that the 1-sample FIT result has a direct influence on the multiple-sample FIT results. In comparison with two Italian studies evaluating the number of FITs, we observed higher PR, PPV and DR for advanced neoplasia (cutoff value 100 ng Hb/mL).[12,17] Potential explanations for these differences included the younger Italian population (aged 50-69 years *vs* 50-74 years), and the higher proportion of female screened individuals (53.8% versus 49.9%).

With respect to sensitivity, it is worth noting that different screening strategies vary more in their impact on the DR of advanced adenomas than of cancer.[10] It is thought that CRCs have a more permanent bleeding pattern than advanced adenomas, which are believed to bleed more intermittently. Therefore it could be hypothesized that with one additional fecal sample (i.e. 2-sample FIT screening), especially more advanced adenomas will be detected. Based on our findings, it can be concluded that 25% of all detected patients with CRC in the 2-sample FIT group had only one positive test. In other words, about 12.5% of CRC cases would have been missed by using 1-sample FIT screening because of intermittent bleeding. When the same calculations are made for the advanced adenomas, 42% of them had just one positive test result. This suggests that 2-sample FIT screening has a larger impact on the detection of extra advanced adenomas than on detecting more CRCs. On the other hand, the extra CRCs could be more important because of the greater urgency to detect them. Furthermore, we showed that five screened individuals would need to be referred for colonoscopy to find one extra advanced neoplasia by means of a second test. Whether this is an acceptable number needed to scope depends on local situations with respect to colonoscopy capacity and on further cost-effectiveness analyses.

This study has some limitations. First, the population under investigation was not invited at the same time. It could be hypothesized that a discrepancy in attendance rate between the different screening strategies could not be observed because of a balance between a difference in intervention (either 1- or 2-sample FIT screening) and a difference in time period and thus maybe more awareness about CRC and CRC screening in general. However, two random samples were taken from exactly the same target population in the southwest of the Netherlands. Since 2006, we have been approaching newly invited individuals for their first CRC screening round and differences in attendance rate were rather small. Therefore, we believe that the main conclusions drawn from this trial are still applicable. Second, this trial only describes results of the first CRC screening rounds with either 1 or 2 FIT samples in a screening-naïve population. Data on attendance and diagnostic yield of successive CRC screening rounds are needed to provide more insight in the long-term (cost)effectiveness of a population-based screening program and the most optimal FIT screening strategy to be used. It could be hypothesized that 2-sample FIT screening may require fewer screening rounds to be as effective as more frequent 1-sample FIT screening when the cumulative sensitivity of several screening rounds, as well as the number of interval cancers found, are compared with each other. In collaboration with the Dutch Comprehensive Cancer Centre, we have started to collect information about interval cancers in screened individuals testing negative by FIT. When these data are completely available, it remains to be shown to what extent the higher diagnostic yield of 2-sample FIT screening reduces the incidence of interval CRCs and therefore might allow longer screening intervals. Third, we only made a comparison between 1-sample and 2-sample FIT screening. We thus do not have any information about the effect of 3-sample FIT screening on attendance and diagnostic yield. A Japanese study reported no additional value of a third sample compared to 2-sample FIT screening.[18] The same conclusion was drawn from a study conducted in Israel.[13] However, the Israeli trial only included patients who were referred for colonoscopy (i.e. both asymptomatic but at increased risk for colorectal neoplasia and symptomatic). Therefore, these data can not be generalized to an asymptomatic average-risk population.

In conclusion, this comparative population-based CRC screening trial shows a similar attendance of 1-sample and 2-sample FIT screening. Two-sample FIT screening using at least one positive test as a cutoff provides a higher detection rate for advanced neoplasia than 1-sample FIT screening. However, this is at the expense of higher positivity rates and thus the need for more colonoscopies. In case of limited colonoscopy capacity, 2-sample FIT screening with the demand for two positive tests has the highest diagnostic yield. Between these two extremes, 1-sample FIT screening is equally effective as

2-sample FIT screening. These results can be used for optimal screening strategy planning, tailored to a range of local needs and colonoscopy capacities that is even wider when also considering 2-sample FIT screening strategies.

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6

Increased risk of adenomas in individuals with a family history of colorectal cancer: results of a meta-analysis

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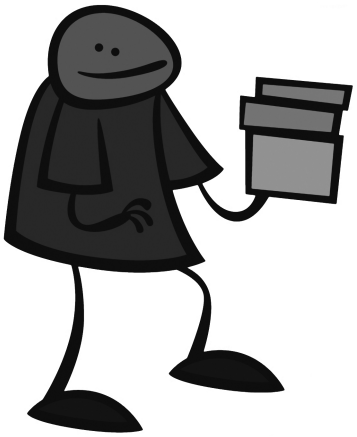

Cancer Causes Control (2010) 21:2287–2293

Abstract

Objective: It is unclear to what extent the increased risk of colorectal cancer in individuals with a family history of colorectal cancer and no known genetic disorders is associated with a higher adenoma prevalence. Our aim is to estimate the relative difference in adenoma prevalence and its age-pattern in individuals with a family history of colorectal cancer compared to those without.

Methods: We performed a literature search to identify colonoscopy studies reporting the adenoma prevalence by age. Using multilevel logistic regression we examined how the adenoma prevalence by age differed between individuals with and without a family history of colorectal cancer. We excluded members of families with a known genetic disorder.

Results: Thirteen colonoscopy studies were identified. The adenoma prevalence was significantly higher in individuals with a family history than in those without (OR 1.7, 95% CI 1.4-3.5). The adenoma prevalence increased with age (OR per year of age 1.06, 95% CI 1.05-1.07). The age trend did not differ significantly between the two groups.

Conclusion: Individuals with a family history of colorectal cancer have a considerably higher prevalence of adenomas compared to individuals without a family history. This is consistent with their increased risk for colorectal cancer.

INTRODUCTION

Individuals with a family history of colorectal cancer (CRC) have approximately a two-fold lifetime risk for the disease compared to the general population.[1-3] The increased cancer incidence is the endpoint of the adenoma-carcinoma sequence.[4] There are clear differences between the development of disease in individuals with genetic disorders and the general population. Individuals with Familial Adenomatous Polyposis develop many more adenomas than the general population, whereas individuals with Hereditary NonPolyposis Colorectal Cancer (HNPCC) have a risk of adenomas that is not nearly as elevated as the risk for cancer. These two genetic cancer groups account for 2-5% of all CRC cases.[5] Approximately 25% of all CRC cases occur in individuals with a family history of CRC and no genetic disorders.[5] Over 10% of the population between ages 30 and 70 has at least one first degree relative diagnosed with CRC.[6,7] For these individuals, it is unclear whether they develop more adenomas, or whether their adenomas are more aggressive. A number of case control studies have reported a higher adenoma prevalence in individuals with a family history compared to those without[8-11] (Odds ratios (OR) varied from 1.5 (95% CI 1.0-2.4)[11] to 3.2 (95% CI 2.1-4.9)[9]) . However, the widely different age distributions are problematic in comparing these studies, given that adenoma prevalence increases with age and the age trend might differ between individuals with and without a family history.

A number of colonoscopy studies have reported the adenoma prevalence for different family risk groups by age. We used these studies to perform a meta-analysis for estimating the relative difference in adenoma prevalence between individuals with and without a family history, and the age-dependency of the difference.

METHODS

Literature search

Colonoscopy studies reporting the proportion of individuals with any adenomas in the general population or in subpopulations of individuals with or without a family history were identified through a PubMed and Embase search for the years 1960 to June 2010. The terms used in the search included "age", "colonoscopy", "adenoma", "polyp", "prevalence" and "risk". The exact search strategy is given in appendix A. Additional articles were searched for via the references cited in retrieved publications.

We restricted the analysis to studies reporting adenoma prevalence for at least two age groups. Studies that did not report the adenoma prevalence separately for indi-

viduals with and without a family history were excluded. Studies or subgroups including individuals with HNPCC or fulfilling the Amsterdam criteria[12], and studies with a majority of individuals having symptoms were excluded. Sigmoidoscopy studies were excluded, and to be able to give a representative estimate of the adenoma prevalence in the colon and rectum, we also excluded colonoscopy studies with a poor reach, defined as less than 50% that reached the cecum. Studies that were limited to large or advanced adenomas were also excluded. To avoid double counting, only one of several studies was included in case their subjects came from the same population in overlapping time frames. We included only full text articles written in English. We used the PRISMA checklist and flowchart to describe the search and its results.[13]

Meta-analysis

The study populations in the selected articles were assigned to the high- or low-risk group. The high-risk group concerned populations with individuals having a family history for colorectal cancer (at least one first degree relative diagnosed with CRC). The low- risk group consisted of populations with individuals with no family history for colorectal cancer.

A logistic two-level model was fitted to the data on adenoma prevalence by age in the high-and low- risk group. To account for the heterogeneity between studies, we applied a two-level bootstrapping technique with 1,000 replicate datasets. The first level (studies) was used to describe differences in background risk between studies. The second level (observations) described differences between age and risk groups within studies. So every replicate dataset was constructed by random sampling with replacement from the studies first, putting more weight on the comparison of observations within one study. On all replicate datasets a standard logistic regression was performed with age, gender and risk group as explanatory variables. The point estimates and confidence intervals of the adenoma prevalence and odds ratios for age, gender and risk group were calculated as mean and percentiles from the results of the 1,000 regressions. If the gender distribution was not given, we assumed 50% males and 50% females. The combined Wald test was used to test for significant interaction between age and risk group. A quadratic relation with age was tested as an alternative to the linear model.

We first estimated the relative difference in adenoma prevalence between risk groups based only on studies that included both a high- and low-risk group. In this analysis, the influence of the heterogeneity between studies was minimized. Next, we repeated the analysis adding all studies with only a high- or low-risk group, to use all information available in the estimation of the age trend in both risk groups.

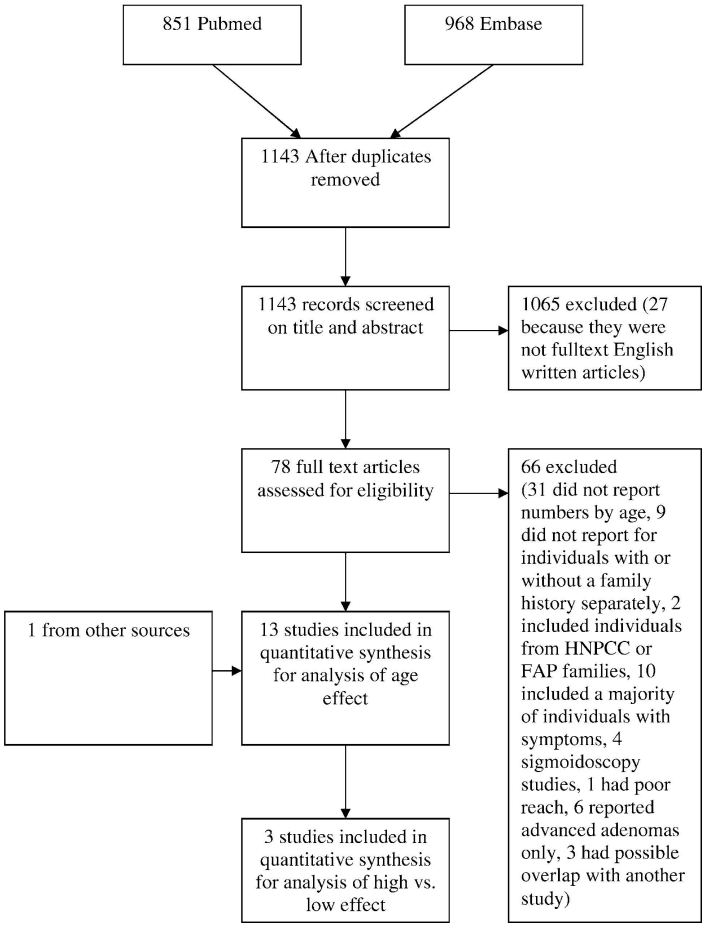

Figure 6-1. Literature review.

RESULTS

Review

The search for Pubmed and Embase provided a total of 1819 citations (Figure 6-1). After adjusting for duplicates 1,143 remained. Of these, 1,038 were discarded because after reviewing the abstracts it appeared that these papers clearly did not meet the criteria. Another 27 studies were omitted because there was no English written full text paper available. The full text of the remaining 78 citations was reviewed. It appeared that 66 did not meet the inclusion criteria. Twelve colonoscopy studies reporting the proportion of individuals with adenomas by age remained.[14-25] One additional study that met the inclusion criteria was identified by searching the reference list of the articles obtained by the database search.[26]

Table 6-1. Characteristics of colonoscopy studies describing adenoma prevalence by age.

Studies	Region (period)	Study population	Screen history
Studies with high- and low-risk individuals			
Guillem (1992)	USA (1980-1990)	181 with FDRs (160 with 1 FDR, 20 with 2 FDRs, and 1 with 3 FDRs), and 83 with no FDRs	no colonoscopy
Regula (2006)	Poland (2000-2005)	10,443 with FDRs (9988 with 1 FDR and 455 with 2 FDRs) and 39705 with no FDRs	no colonoscopy in the last 10 years
Tung (2000)	Taiwan (1994-1997)	234 with FDRs (210 with 1 FDR, 24 with more) and 468 with no FDRs	no
Studies with high-risk individuals			
Dove-Edwin (2005)	United Kingdom (1987-2003)	1,024 with 1 or 2 FDRs	first colonoscopy
Dowling (2000)	Australia	232 with 1 or 2 FDRs	first colonoscopy, some had FOBT before
Grossman (1988)	USA (1980-1986)	154 (108 with 1 FDR and 46 with 2 FDRs)	first colonoscopy, 77% had sigmoidoscopy before
Hunt (1998)	United Kingdom (1991-1993)	83 with 1 or 2 FDRs	unknown
Sauar (1992)	Norway (1989)	156 with at least 1 FDR	unknown
Syrigos (2002)	United Kingdom (1992-1997)	249 (212 with 1 FDR and 37 with 2 FDRs)	no colonoscopy in the last 5 years
Wu (1995)	Taiwan (1992-1994)	213 (210 with 1 FDR, 3 with 2 FDRs)	first colonoscopy
Studies with low- risk individuals			
Johnson (1990)	USA	90 with no FDRs	no colonoscopy in last 3 years
Rundle (2008)	USA (2004-2006)	905 with no FDRs	unknown
Soon (2008)	Taiwan (2004-2006)	1,382 with no FDRs	No endoscopy in the last 5 years

FDR = First Degree Relative

The study characteristics of the studies that reported adenoma prevalence by age are given in Table 6-1. Seven studies were published between 2000 and 2010 and all were published after 1988. Five studies were conducted in Europe, four in the United States, three in Asia, and one in Australia. Having one first degree relative with colorectal cancer was the least restrictive definition for family history used in the studies. Some studies used a higher number of affected relatives or restricted the age of diagnosis of the relative. Two subgroups were excluded from our analysis. The first group is the one included by Dove-Edwin[14] that fulfilled Amsterdam Criteria. The second group is the group included by Hunt,[18] from families with three or more first degree relatives that contained families with HNPCC.

Three studies included reported the adenoma prevalence in individuals with and without a family history separately.[17,20,24] The study groups were assigned to the high- and low-risk group respectively.

Seven studies reported the adenoma prevalence in individuals with a family history

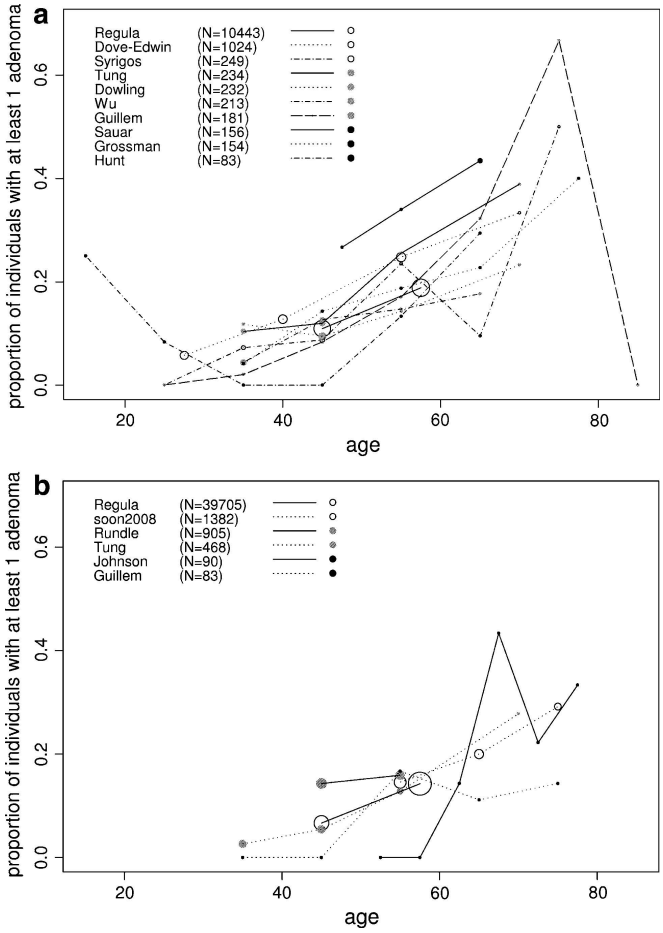

Figure 6-2. Proportion of individuals with at least one adenoma. The highrisk group in A and the low-risk group in B. Dot size is scaled with the number of subjects.

only and were added to the high-risk group.[14-16,18,22,25,26] The adenoma prevalence of the risk group is presented in Figure 6-2a. Generally, the adenoma prevalence increases with age, except for some studies with small sample sizes.[15,17,18,26] Sauar and Tung both invited individuals via a FDR diagnosed with CRC. Although a minority of individuals with bowel symptoms was invited, the symptoms were not the primary reason to have a colonoscopy.

Three studies that included only individuals with no FDRs with CRC were added to the low-risk group.[19,21,23] The adenoma prevalence by age in the low-risk group is shown in Figure 6-2b. The adenoma prevalence is comparable between studies, except for two small studies.[17,19] The adenoma prevalence between ages 40 and 49 reported

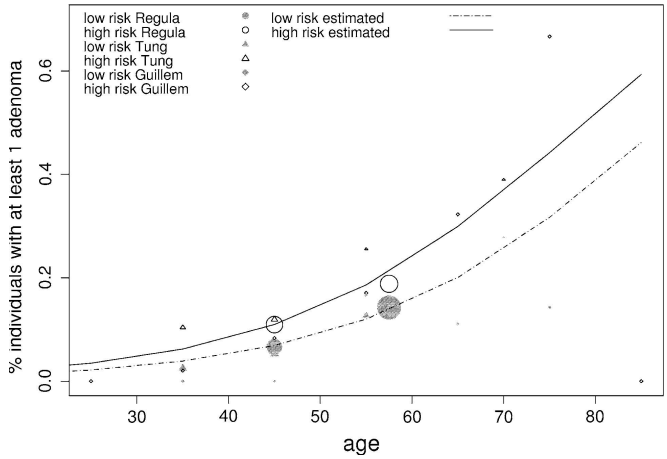

Figure 6-3. Estimated and observed proportion of individuals with at least one adenoma per risk group. Dot size is scaled with the number of subjects.

by Rundle is remarkably high. Although these individuals reported to have no affected FDRs and no bowel symptoms, they might have reasons to consider themselves at elevated risk of CRC, given that average risk individuals are usually not advocated to have a screening colonoscopy at this age in the United States of America. The individuals included by Regula between ages 40 and 49 have a family history for cancer other than colorectal, which may possibly be associated with an increased risk for colorectal cancer and adenomas.

Meta-analysis

The results of the analysis that included only studies with both a high- and a low-risk group are shown in Figure 6-3. The regression model used had a linear relation with age (a quadratic relation with age did not improve the fit significantly, data not shown). The adenoma prevalence was significantly higher in the high-risk group than in the low-risk group (OR 1.7, 95% CI 1.4-3.5). A higher proportion of males in the population was also associated with a higher adenoma prevalence, but not significantly (Table 6-2). The adenoma prevalence increased significantly with age (OR 1.06 per year of age, 95% CI 1.05-1.07). The adenoma prevalence estimates by age and risk group can be found in Appendix B.

When we repeated the analysis after adding the studies with only a high-or a low-risk group, the age trend did not change (Table 6-2). Thus, the age trend was confirmed by the studies added to the analysis. When we allowed the trend over age to vary by risk group, the trend turned out to be very similar for both risk groups ($p>0.05$).

Table 6-2. Results of logistic regression on adenoma prevalence data by age, gender and risk group.

Predictor	OR (95% CI)	
	Analysis of high versus low effect (3 studies)	Analysis of age effect (13 studies)
Age*	1.06 (1.05 - 1.08)	1.06 (1.05 - 1.07)
Gender (% male)	3.0 (0.4 -144)	3.2 (0.8 – 28)
High-*vs* Low- risk group	**1.7 (1.4 - 3.5)**	1.7 (1.4 - 3.1)

* For all risk groups, for every year T+1 versus year T

DISCUSSION

Having first degree relatives with CRC is associated with an increased risk of having adenomas (OR 1.7). Adenoma prevalence increases with age (OR 1.06 per year of age). We did not find a significant difference in age trend between the high- and low-risk groups.

The CRC risk in the background populations differs between studies, given the different regions and time periods. Another difference between studies that influences the adenoma prevalence is the exclusion criteria for screen history and symptoms. The comparison of risk groups or age groups within one study is not influenced by these study differences. In the analysis, we took these considerations into account by using "study" as a first level in a two-level approach instead of directly estimating odds ratios over all observations. To further prevent bias from risk differences between studies, we estimated the difference between risk groups using only studies with both a high- and low-risk group. For the estimation of the age trend, we added the studies with only a high- or a low-risk group. In both analyses, a study from Poland was the largest study by far, which caused the similar results in age trend.

The problem of comparing the adenoma prevalence from different studies was illustrated by the group of studies that reported the adenoma prevalence in an unidentified mixture of individuals with and without a family history. The differences in adenoma prevalence between these studies were substantial (and varied between 0.14[27] and 0.33[28] at age 55 for example). Some Asian studies reported relatively high adenoma prevalence,[28-30] and a German study relatively low.[31] This is the opposite of what one would expect based on the CRC incidence in these countries. The difference might be partly explained by different (often unreported) percentages of individuals with a family history.

There are other issues that may influence our findings. Individuals tend to under-

report their family history.[32,33] This would result in underestimating the difference in adenoma prevalence between individuals with and without a family history. Also, the observed adenoma prevalence is based on findings at colonoscopy and adenomas may have been missed. False negative results are more likely in low-risk individuals than in high-risk individuals because high-risk individuals have relatively more large adenomas[8,10,11,24], and they have more often multiple adenomas.[20] The difference in false negatives will result in an overestimate of the difference in adenoma prevalence. For example, the odds ratio in the Tung study would decrease from 2.3 to 2.2 if 20% of the individuals with only small adenomas remained undetected.

The estimated odds ratio of 1.7 for adenoma prevalence in individuals with a family history compared to those without is in line with results of case control colonoscopy studies.[8-11] Reported odds ratios ranged from 1.5 (95% CI 1.0-2.4)[11] to 3.2 (95% CI 2.1-4.9)[9] for having at least one first degree relative.

The reported increased risk of CRC in individuals with a family history compared to those without is 2.25 (95% CI 1.86-2.73).[1] The relative risk (RR) of having adenomas is smaller than the OR and depends on the adenoma prevalence. A prevalence of 20% in the low- and 30% in the high-risk group for example corresponds to an OR of approximately 1.7 and to a RR of 1.5. A constant OR over age, as resulted from our analysis, corresponds to a decreasing RR due to the increasing adenoma prevalence. The observed RR for CRC also decreases with age.[1] To compare the RR for adenoma prevalence with the RR for CRC, an uncertain time lag should be taken into account.

The adenoma prevalence in individuals with a family history is clearly elevated compared to those without and thus helps to explain the increased cancer risk (RR) of 2.25 at least to some extent. The remaining gap can be explained by plausibly assuming that the high-risk group not only includes more individuals with adenomas, but that these individuals also have a higher mean number of adenomas.[34] Only few adenomas will develop into cancer, and having more adenomas increases the chance of having one that does so, thereby increasing the risk for CRC. There is possibly some room left for the hypothesis that the increased risk of CRC is not entirely caused by more adenomas, but also by a faster development of (some) adenomas. Besides, not all cancers develop through the adenoma-carcinoma sequence. Thus, a remaining gap could also be closed by a higher proportion of cancers that develops through alternative pathways in individuals with a family history.

The higher adenoma prevalence in individuals with a family history implies the start of CRC screening at a younger age and using a somewhat smaller screen interval because of the mentioned shorter mean time until the first adenoma becomes cancer in an individual. A faster development of the adenomas would more favor a shorter screen

interval. How much earlier screening should start and how much shorter the interval should be, can be explored using models that simulate adenoma onset and dwell times, using the results of the presented analysis.

In conclusion, individuals with a family history of CRC have a considerably higher adenoma prevalence compared to individuals without a family history. This is consistent with the increased risk for CRC.

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APPENDIX A: SEARCH STRATEGY PUBMED

1. Age [tw]
2. Polyp [tw]
3. Polyps [tw]
4. Adenoma [mesh]
5. Adenom*[tw]
6. 2 or 3 or 4 or 5
7. Colon [tw]
8. Colonic [tw]
9. Colorect*[tw]
10. Rectum [tw]
11. Rectal [tw]
12. 7 or 8 or 9 or 10 or 11
13. Prevalence [tw]
14. Risk [mesh]
15. Risk [tw]
16. 13 or 14 or 15
17. Colonoscopy [mesh]
18. Colonoscopy [tw]
19. 19 17 or 18
20. 1 and 6 and 12 and 16 and 19

APPENDIX B

Appendix table 6-1. Estimated adenoma prevalence by age and risk group based on three studies with high-and low-risk groups

Age	**15**	**25**	**35**	**45**	**55**	**65**	**75**	**85**
Adenoma prevalence								
Low risk	0.01	0.02	0.04	0.07	0.12	0.20	0.32	0.46
CI (95%)	0.00–0.02	0.01–0.03	0.02–0.05	0.03–0.09	0.06–0.15	0.12–0.25	0.20–0.39	0.32–0.55
High risk	0.02	0.03	0.06	0.11	0.19	0.30	0.44	0.59
CI (95%)	0.01–0.03	0.02–0.04	0.04–0.08	0.09–0.13	0.15–0.23	0.24–0.37	0.35–0.56	0.48–0.74

50% is assumed male

7

A decision-analytic evaluation of the cost-effectiveness of family history-based colorectal cancer screening programs

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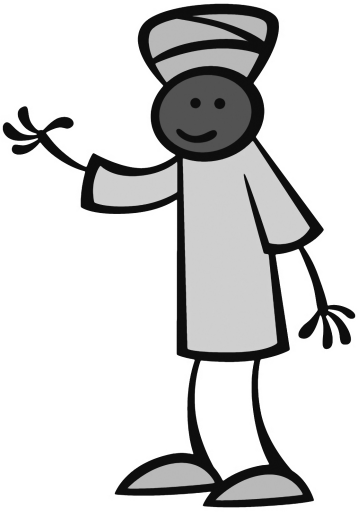

Am J Gastroenterol 2010; 105:1861–1869

ABSTRACT

Objectives: The aim of this study was to determine the cost-effectiveness of family history screening (FHS) for colorectal cancer (CRC) susceptibility at age 40 with early screening of those with increased risk.

Methods: The cost-effectiveness of several family history-based screening programs was estimated with a validated microsimulation model, using data from the SEER cancer registry, life tables, medicare records, and published data. Familial cancer syndromes were excluded. Screening programs evaluated included (i) colonoscopy screening every 10 years starting at age 50 (no family history assessment); (ii) colonoscopy every 10 years from age 40 for persons with a family history; (iii) colonoscopy every 5 years from age 50 for those with a family history; and (iv) colonoscopy every 5 years from age 40 for persons with a family history. In each FHS scenario, persons without a family history are screened with colonoscopy at age 50, then every 10 years to age 80.

Results: Compared with colonoscopy screening of all persons from age 50, the cost-effectiveness of the family history-based screening programs varied from $18,000 – $51,000 per life year (LY) gained. Screening family history cases every 5 years from age 40 is more cost-effective than screening every 10 years from age 40. Reducing screening frequency for those without a family history lowers program expenditures substantially at a modest loss of LYs. The results are sensitive to the CRC risk difference between positive and negative family histories.

Conclusions: The cost-effectiveness of CRC FHS guidelines varies widely. Economic issues should be considered before implementing family history-directed screening programs.

INTRODUCTION

Persons having a first-degree relative (FDR) with colorectal cancer (CRC) are at increased risk for developing cancer. Family history reflects several genes of higher prevalence and environmental exposures with interactions. Screening persons for family history may identify large numbers of persons who would benefit from earlier or more aggressive cancer screening. Accordingly, several clinical practice guidelines recommend that persons meeting family history criteria should begin CRC screening at an earlier age than the general population.[1-4]

Family history assessment is not practiced uniformly in clinical settings, although programs have been started to increase personal family history awareness in the general population.[5] The American Cancer Society, Canadian Task Force on Preventive Health Care, US Preventive Services Task Force, and American Gastroenterological Association have published guidelines for screening persons with a family history of CRC, and several alternatives have been proposed (Table 7-1).

Although there is a rationale for earlier screening of persons with a family history, as risk has been shown to be higher at younger ages,[6] no direct evidence exists support-

Table 7-1. Current guidelines for determining increased risk for CRC based on family history and screening recommendations[a]

Source	Risk categories	Screening schedule
American Gastroenterological Association[1]	≥ 2 First-degree relatives with CRC / AdP, or ≥ 1 first-degree relative affected before age 60	Colonoscopy every 5 years, beginning at age 40 or 10 years before youngest diagnosis in family, whichever came first
	1 First-degree relative affected with CRC / AdP at or after age 60[a]	Same as average risk, but beginning at age 40
American Cancer Society[2]	CRC or AdP in ≥1 first-degree relative before age 60 or ≥ 2 first-degree relatives at any age (excluding HNPCC and FAP)	Colonoscopy every 5 – 10 years, starting at age 40
Canadian Task Force on Preventive Health Care[3]	1 Or 2 first-degree relatives with CRC	Same as average risk
	> 2 Relatives with CRC	Consider genetic screening
US Preventive Services Task Force[4]	≥1 First-degree relative with CRC onset before age 60	Any screening modality, starting at age 40

AdP, adenomatous polyp; CRC, colorectal cancer; FAP, familial adenomatous polyposis coli syndrome; HNPCC, hereditary nonpolyposis colorectal cancer.
a Excludes criteria identifying persons with familial cancer syndromes, who are at very high or extreme risk.

ing the efficacy or cost-effectiveness of early screening. Population-wide family history assessment carries substantial clinical and economic implications, as tens of millions of adults would be assessed and 10 – 15% of those evaluated would likely meet the criteria for more aggressive screening.[1,6,7] Implementing family history programs would also greatly impact primary care physicians, specialists, and public and private health-care payers.

To assess these issues better, we used a validated microsimulation model to evaluate the clinical and economic implications of implementing one of the CRC family history screening (FHS) programs recommended by major organizations, followed by tailored screening based on the results. We do not address the costs and benefits of assessment for rare Mendelian disorders, such as familial adenomatous polyposis coli and hereditary nonpolyposis colorectal cancer (Lynch Syndrome), as they have been discussed elsewhere.[8-11]

METHODS

We evaluated clinical outcomes and cost-effectiveness for FHS for CRC compared with Usual Care in a population of individuals who have not had FHS. Usual Care is defined as inviting all persons at age 50 for screening colonoscopy, and if normal, repeating screening every 10 years. Under FHS, persons at age 40 are asked about FDRs with CRC. A "positive" family history is defined by the American College of Gastroentrology (Table 7-1), with the exception that we do not include relatives with known high-grade adenomatous polyps, because of the difficulties in determining the population prevalence of these individuals, and exclude persons with familial cancer syndromes (i.e., adenomatous polyposis coli or Lynch Syndrome) who are invited to begin screening with colonoscopy at age 40. Thus, for this model, a positive family history of CRC is defined as one FDR diagnosed with CRC under the age of 60, or two FDRs diagnosed at any age. As the "average-risk" population is comprised of persons with and without a family history of CRC, removing persons with a family history from the population implies that those in the remaining population would have slightly lower risk for developing CRC. The model adjusts risk downward modestly for the individuals without a family history.

Population and perspective

The simulation is constructed as a dynamic population model; each year a cohort of people at age 40 who have not undergone FHS enter the model. Persons face two alter-

natives: "Usual Care" or FHS (described below). Persons in either scenario can develop adenomatous polyps and CRC (only after developing an adenomatous polyp), and can die from CRC or other causes. Persons can develop secondary adenomas or cancers after definitive treatment. Birth tables and life tables are constructed so that the simulated population reflects the US population in 1993 with births between 1893 and 1993.

The analysis is conducted from the societal perspective. This study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Screening scenarios

In the Usual Care scenario, colonoscopy screening is offered to the entire population at ages 50, 60, 70, and 80, without considering family history. We then considered several alternative screening schedules for those whose FHS finds one FDR diagnosed with CRC before age 60 or two FDRs with CRC diagnosed at any age, excluding familial cancer syndromes (We are unable to model scenarios where individuals have relatives with a history of advanced adenomas, because of lack of population data; shorthand descriptions denoted in parentheses):

1. Screening colonoscopy at age 40, then every 10 years to age 80 (40/10)
2. Screening colonoscopy at age 50, then every 5 years to age 80 (50/5)
3. Screening colonoscopy at age 40, then every 5 years to age 80 (40/5)

In each FHS scenario, persons without a family history are screened with colonoscopy at age 50, then every 10 years to age 80.

In all scenarios, the surveillance schedule depends on the findings at the last colonoscopy. Thus, if a polyp is detected, a 5-year repeat endoscopy is scheduled regardless of the initial screening strategy.

Model structure

The model used to address the questions is the MISCAN - COLON model, a microsimulation model designed to evaluate costs and outcomes of CRC screening. The model was developed by the Department of Public Health at the Erasmus University Rotterdam, The Netherlands, in cooperation with the National Cancer Institute.[12]

The model was modified to include FHS starting at age 40. The disease stages are distinguished in the adenoma-carcinoma sequence. Most adenomas will never grow into cancer. Owing to genetic and behavioral factors (e.g., diet), adenomas develop at an earlier age in persons with a family history compared with those without a family history; these adenomas also may have a greater propensity to develop into invasive carcinomas.[13] Several studies have shown a higher prevalence of adenomas in individuals

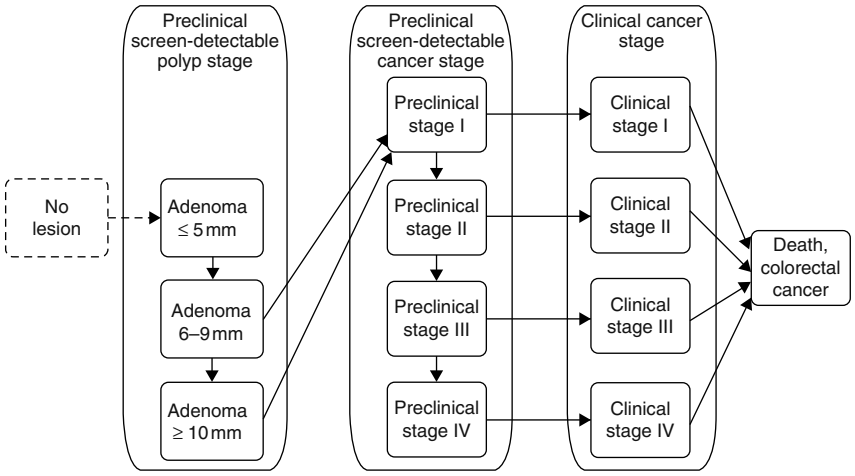

Figure 7-1. Adenoma and cancer stages in the MISCAN-COLON microsimulation model. The size-specific prevalence of adenomas, as well as the proportion of adenomas that develop into cancer, is dependent on age and family history for colorectal cancer.[1]

with a positive family history compared with those individuals with a negative family history.[14-18]

We model a proportionally increased hazard rate that leads to a shift of the proportion of adenomas with earlier ages of onset in persons with a family history. Polyp dwell times are assumed to be the same. Invasive cancers can and will eventually be clinically diagnosed, but a person may die of other causes before reaching diagnosis (Figure 7-1).

The preclinical and clinical invasive cancer stages at detection are subdivided into American Joint Committee on Cancer/International Union against Cancer stages I - IV.[19] Details of the model structure and assumptions as applied to screening colonoscopy in average-risk persons have been published elsewhere.[20]

Reference data

Table 7-2 lists inputs (base case and ranges) and input sources for the model. Using history prevalence studies, we assume that 2% of persons meet family history guidelines regarding FDRs with CRC (one FDR diagnosed before age 60 or two or more FDRs of any age).[21] Given the literature about the accuracy of CRC family history reporting, we assumed that, among those reporting family history, 30% are inaccurately "negative," whereas false-positive reports are rare.[22] On the basis of a recent metaanalysis of studies on CRC risk in families with a CRC history compared with individuals without a family history,[23] those with family histories meeting American College of Gastroenterology

criteria for early screening were modeled to have an increased CRC risk compared with the average-risk population (relative risk (RR) = 3.80). In the sensitivity analysis, we varied the RR between 1.9 and 5.7 depending on the particular compositions of relatives with CRC (e.g., one FDR over age 60 *vs* two FDRs of any age). In all cases, increased risk was modeled by multiplying the adenoma incidence with the CRC RR compared with the average-risk population. To adjust to the total risk in the population the adenoma incidence rate was lowered for those without a family history (RR = 0.94).

Colonoscopy is assumed to be 75 - 95% sensitive and 100% specific for detecting adenomatous polyps.[24,25] The rate of nonfatal complications by bowel perforation during colonoscopy is assumed to be 2.4 per 1000 colonoscopies carried out.[26,27] The rate of mortality from complications after colonoscopy is assumed to be < 0.1%.[28]

Survival after a CRC diagnosis is based on CRC patient survival recorded in the Survey Epidemiology and End Results database.[29] Stage-specific CRC survival of patients with screen-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage.[11] Complete removal of an adenoma always prevents development of any subsequent cancer that may arise from that adenoma.

Base case values for costs of FHS and CRC screening with colonoscopy are based on medicare fee schedules. Our base case assumes that one-third of a level III (history/exam) office visit is used to take the family history. We assume a 2-h time cost for the patient and driver associated with traveling to and from colonoscopy and time spent during the procedure. Patient time costs are valued using 2006 United States national median hourly wage estimates.[30] Treatment costs of adenomas found during screening or surveillance are assumed to consist only of costs for polypectomy and pathology. On the basis of recent studies, the risk of colonoscopyrelated complications is assumed to be 2.4/1,000, with an average cost $5,500, assuming that 30% of the complications are perforations.[28,31,32]

Costs of care for persons with CRC are based on the published literature.[33-37] Patient time costs associated with cancer treatment are based on published estimates.[38] All costs are expressed in real terms in 2005 US dollars. Future expenditures and life years (LYs) are a discount to present value at an annual rate of 3%, as recommended by the Panel on Cost Effectiveness in Health and Medicine.[39]

Model outcomes

Outcomes for the intervention and Usual Care arms are stated as the number of screening tests and colonoscopy surveillance tests carried out, number of deaths prevented, and number of life years gained (LYG).

Table 7-2. Base case values, ranges, distributions, and citations for the family history screening at age 40 compared with Usual Care[a]

Parameter	Base case	High	Low	Distribution	Reference
Costs of FHS screen test	$35	$70	$17.5	Lognormal	48
Sensitivity FHS	70%	90%	50%	Beta	22
Specificity FHS	99%	100%	97%	Beta	22
CSCPY (nothing)	850	1,700	425	Lognormal	48
CSCPY (lesion)	1,075	2,150	500	Lognormal	48
Sensitivity CSCPY	Aden < 5 mm 0.8, 6-9 mm 0.85, 10+ and cancer 0.95	All 100%	Aden < 5 mm 0.75, 6-9 mm 0.8, 10+ and cancer 0.9	Beta, correlated	24,25
Percentage of complications during screen test	0.0024 (0.0001 with death as result)	0.0048	0	Beta	26-28
Cost of complications of screen test	$5,500	$11,000	$2,750	Lognormal	31,32
Adherence to CSCPY screening, low risk	50%	80%	25%	Beta	49
Adherence to CSCPY screening, high risk	80%	100%	50%	Beta	49
Incidence of polyps + FHS	3.8[b] (comp to avg)	5.7	1.9	Lognormal	23,47
% With FHS in population	2%	4%	1%	Beta	21
Colorectal cancer				Lognormal	33-37
Initial treatment					
Stage I	$23,000	$28,000	$19,000		
Stage II	$32,000	$39,000	$26,000		
Stage III	$39,000	$47,000	$32,000		
Stage IV	$51,000	$80,000	$42,000		
Further treatment					
Stage I	$1,800	$2,200	$1,500		
Stage II	$1,700	$2,100	$1,400		
Stage III	$2,500	$3,000	$2,000		
Stage IV	$7,600	$9,300	$6,300		

Parameter	Base case	High	Low	Distribution	Reference
Palliative care, colorectal cancer deaths					
Stage I	$41,500	$50,000	$34,000		
Stage II	$41,500	$50,000	$34,000		
Stage III	$43,500	$53,000	$36,000		
Stage IV	$58,500	$71,000	$48,000		
Palliative care deaths, other cause					
Stage I	$10,000	$12,000	$8,000		
Stage II	$9,000	$11,000	$7,400		
Stage III	$12,000	$15,000	$10,000		
Stage IV	$32,000	$39,000	$26,000		
Patient time costs				Lognormal	38
Initial treatment	$5,200	$5,900	$3,900		
Further treatment	$340	$380	$260		
Palliative care	$3,200	$3,600	$2,400		
Patient time and transport cost per screening	$99 ($81 + 18)	$198	$49.50		30
5-Year relative survival, colorectal cancer, by stage				Lognormal	29
Stage I	92.2%	94%			
Stage II	82.6%	85%			
Stage III	61.3%	67%			
Stage IV	7.9%	16.7%			

CSCPY, colonoscopy; FHS, family history screening.

a See text for the definition of the family history screening and Usual Care. These data refl ect the FHS 40 / 10 screening option.

b RR = 4 compared with negative family history individuals (47) corresponds to RR = 3.8 compared to average risk.

Sensitivity and uncertainty analysis

We carried out one-way sensitivity analysis and multi-way uncertainty analyses on the model parameters. For the one-way analysis, values were varied across range assumptions or the 95% range in cases where a confidence interval was available. In cases wherein distributions were not available for individual parameters, we used lognormal for cost parameters and β distributions for other parameters. Parameters for the one-way analysis were ordered from most to least influential on the final outcome, incremental cost-effectiveness ratio values. To describe the uncertainty in the estimates of cost-effectiveness, we constructed cost-effectiveness acceptability curves applying the bootstrap method with 1,000 replication runs.[40]

RESULTS

Table 7-3 lists the outcomes and costs for no screening, Usual Care (population wide screening starting at age 50), and the three alternative screening schedules after FHS. All FHS schedules provide more LYs and are more costly than Usual Care. FHS followed by screening every 5 years beginning at age 40 (40/5) is the most costly option, but also provides the highest number of LYs of all strategies. Total lifetime costs and LYG are very similar for the 40/10 and 50/5 strategies.

Table 7-4 lists the incremental cost-effectiveness of FHS strategies compared with no screening and Usual Care. The incremental cost-effectiveness of the FHS 40/10 option *vs* Usual Care (50/10) is $122,000 per LYG. The relatively unfavorable cost-effectiveness is because of the small yield in additional years of life and small gain in treatment costs, at a substantial increase in program and screening costs, compared with population-wide screening at age 50. In addition, FHS strategies 40/10 and 50/05 are dominated compared with alternatives (higher costs, inferior LYG). FHS strategy 40/5 is the most cost-effective strategy compared with Usual Care with an incremental cost-effectiveness of $51,000 per LYG. Although it seems counterintuitive that strategy 50/05 is dominated given that starting at age 40 is not very cost-effective with an interval of 10 years, but is with an interval of 5 years, the explanation is that having additional costs for FHS is relatively unfavorable with only one additional screening at age 40. If one has already incurred FHS costs at age 40, the more aggressive screening strategy (every 5 years) dominates delaying this strategy until age 50.

Sensitivity and uncertainty analysis

Comparing the FHS 40/10 with Usual Care, the most influential parameters in the one-way sensitivity analysis were, in order from greatest to least: costs of colonoscopy with-

Table 7-3. Lifetime costs and effects from the societal perspective, per thousand 40-80 year-old in 2000[a]

	No screen	Usual Care	Family history screen age 40		
Screening schedules for positive family history, otherwise 50/10		**50/10**	**40/10**	**50/5**	**40/5**
Outcomes					
Screening tests	0	983	997	1001	1,027
Surveillance tests	0	295	296	299	301
Colorectal cancer deaths	23.29	17.37	17.35	17.31	17.28
Life years	48,285	48,350.46	48,350.76	48,351.16	48,351.69
Lifetime costs (thousands)					
Family history screenings	0	0	24.9	24.9	24.92
Screening tests[b]	0	1,593.40	1,607.40	1,611.70	1,639.16
Surveillance tests[b]	0	406.90	408.20	410.60	412.98
Diagnostics screening	0	0	0	0	0
Clinical diagnostics	62.3	45.0	45.0	44.8	44.77
Treatment of side effects	0.8	17.4	16.9	17.7	18.08
CRC treatment	3,701.10	2,962.1	2,959.50	2,953.8	2,949.25
Patient time cost for treatment	505.3	432.8	432.60	432.00	431.55
Total lifetime cost (including Family History)	4,269.40	5,457.60	5,495.20	5,495.60	5,520.71
Short-term cost (thousands)					
Total costs year 1	105	132	133	133	134
Total costs years 1 – 5	112	139	140	140	141
Life years gained *vs* no screening	NA	65.76	66.07	66.46	66.99

CRC, colorectal cancer; NA, not applicable.
a See text for the definition of Usual Care, 40 / 10, 50 / 5, and 40 / 5.
b Patient time costs for colonoscopies are included

Table 7-4. Incremental cost-effectiveness ratios for colorectal cancer screening considering Usual Care (no family history screening) and alternative schedules following family history screening, all using colonoscopy; comparison groups appear within table, all amounts are in 2005 US dollars[a]

Strategy	**Usual Care 50/10**	**FHS 40/10**	**FHS 50/5**	**FHS 40/5**
No screening	18,069	18,555	18,449	18,678
Usual Care 50/10		121,722	53,727	51,022
FHS 40/10			896	27,455
FHS 50/5				47,411
FHS 40/5				

FHS, family history screening.
a See text for the definition of Usual Care, 40/10, 50/5, and 40/5.

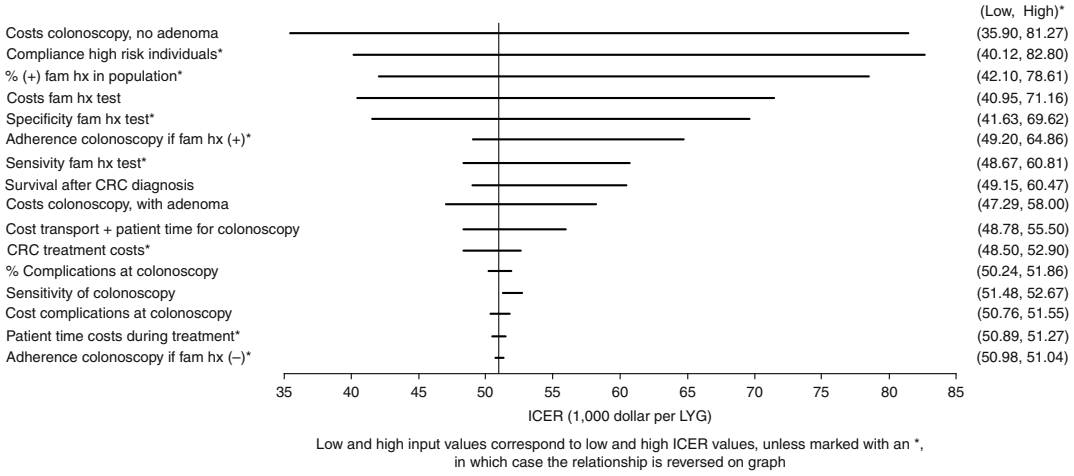

Figure 7-2. One-way sensitivity analysis. This plot reflects the effect of the most influential input variables on the incremental cost-effectiveness ratio (ICER, or the cost per year of life gained) of colorectal cancer (CRC) family history screening (FHS) at age 40 followed by colonoscopy in those with a positive family history vs. Usual Care (population screening at age 50). The values in parentheses show the ICERs at the maximum and minimum value for each input. Table 2 displays the maximum and minimum values for each parameter. The vertical line shows the ICER when all input variable values are set at their base values.

out adenoma, compliance by high-risk individuals, and the percentage of people in the population with a positive family history (Figure 7-2). Many parameters influenced the incremental cost-effectiveness ratio in a nonlinear way; i.e., had varying impacts on the cost-effectiveness of the strategy across the range from minimum to maximum values. The nonlinearity is because of the relationship between interventions and effects. As the specificity of family history falls, more individuals are screened as if they are at increased risk. Compliance then increases because of perceived increased risk, resulting in higher initial costs that decrease rapidly for alternative strategies compared with Usual Care. However, LYG decrease as specificity falls, because these individuals are not actually at increased risk.

The multi-way analysis (cost-effectiveness acceptability curves) is shown in Figure 7-3. Usual Care *vs* no screening shows the least amount of overall uncertainty (steepest curve), whereas the FHS 40/10 *vs* no screening shows the greatest uncertainty (flattest curve). FHS 50/5 is dominated in 35 of 1,000 runs. Usual Care is dominated in 209 of 1,000 runs, whereas FHS 40/10 is dominated in 998 of 1,000 runs. FHS 40/5 is dominated in 0 of 1,000 runs.

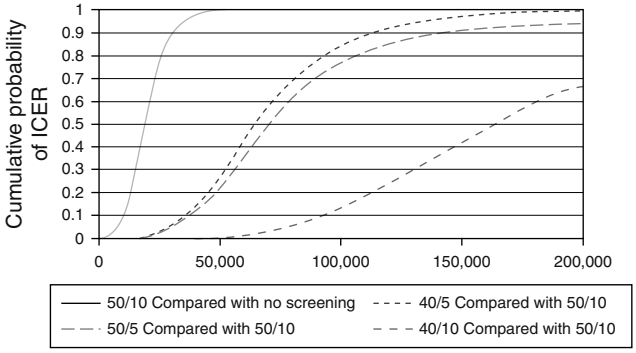

Figure 7-3. Cost-effectiveness acceptability curve for the strategies with the most favorable incremental cost-effectiveness ratios (ICERs). The family history screening (FHS) 40/10 strategy was always dominated and the FHS 50/05 strategy was dominated in the majority of runs, thus ICER values were plotted compared with Usual Care (50/10). The curves represent the probability that the technology is cost-effective at the threshold willingness-to-pay value per life year gained (x axis).

DISCUSSION

Several expert groups advocated FHS followed by tailored CRC screening, but the clinical and economical implications of such a program have not been established. Using a validated micro-simulation model, we found that FHS at age 40, followed by colonoscopy schedules following current guidelines, has moderate-to-poor cost-effectiveness when compared with population-wide screening at age 50. For persons identified as having higher risk based on family history, 5-year screening schedules appear to have superior cost-effectiveness to 10-year schedules.

Our findings have implications for screening policy as researchers, clinicians, and policymakers work to make family history a more prominent part of general evaluations for persons approaching the age where CRC screening is recommended. All strategies have cost-effectiveness ratios that most US decision makers would find acceptable when compared with no screening. Compared with each other and to Usual Care (colonoscopy every 10 years from age 50), the incremental value varies widely.

We note several limitations in our analysis. First, family history evaluations are not typically focused on CRC alone. We do not account for benefits and costs that might accrue from FHS for other diseases. In addition, our analysis focuses on patients for whom family history is not recorded. Physicians who have recorded family history information might simply update the histories when their patients turned 40. In this case,

FHS may cost less than our base assumption. The cost of FHS is moderately influential to the overall cost-effectiveness of the program (Figure 7-2); at a cost of $17, the cost-effectiveness of FHS is approximately $90,000 per LYG (Figure 7-2).

Second, the model does not account for the positive and negative quality of life impacts associated with screening, early detection, and CRC. Third, we do not consider screening with other modalities, such as flexible sigmoidoscopy and fecal occult blood testing, as colonoscopy is rapidly becoming the preferred screening modality in the United States and is generally the recommended test for persons at increased risk.

Fourth, our model is based on an assumption that the mechanism behind the earlier and higher observed incidence of CRC among persons with a family history is increased polyp incidence at an early age. In reality, increased aggressiveness of polyps (e.g., reduced dwell time and/or greater rate of cancerous transformation) may also havea role. While we do have a relatively high percentage of persons in the model with short polyp dwell times, we acknowledge that this does not fully characterize the complexity of the situation.

Fifth, our model assumes that all cancers develop from polyps. As some cancers may not develop from polyps, this increases the apparent effectiveness of overall screening. Furthermore, strategies with more frequent screening schedules would have better apparent cost-effectiveness relative to less frequent strategies, as each colonoscopy exposes the patients to risks and costs without additional benefit.

Sixth, we assume that colonoscopy is 100% specific for identifying adenomatous polyps. Lower rates of specificity will result in pathology costs, but will not improve screening outcomes. In the uncertainty analysis, specificity of colonoscopy was not a highly influential factor. Finally, we do not include potential quality of life decrements associated with knowledge of one's family history in the model.

There is substantial variance among the current guidelines for risk stratification based on family history (Table 7-1). Some have argued for refinements with regard to the age at onset of screening. After finding no cancers and an extremely low prevalence of adenomas among a cohort of CRC patients' relatives in Scotland judged to be at "moderate risk" by current Scottish colorectal screening guidelines, Bradshaw *et al.*[41] proposed that screening need not begin before age 50. Syrigos *et al.*[42] found that asymptomatic relatives with a family history of CRC and metaplastic polyps had a threefold increased risk for the existence of synchronous adenomas when compared with asymptomatic individuals with a family history of CRC without metaplastic polyps. This study team recommended modifying guidelines to include close relatives of persons with a history of adenomas but no cancer. With regard to screening frequency, based on the findings of their surveillance study in a Swedish population with a family and personal

history of polyps, Lindgren *et al.*[43] recommended colonoscopy every 3 – 5 years among persons with two close relatives with CRC.

There is an intuitive appeal to designing screening policies based on risk. Higher-risk persons stand to gain the most from screening, whereas less intensive screening of lower-risk persons saves societal resources and exposes persons to fewer procedures (with their attendant risks) at a relatively small loss in terms of fewer cancers detected. Nevertheless, we realized that some may not accept the concept of tailoring screening to maximize efficiency if the result has fewer potential benefits for some population segments, even if the loss in LYG is slight. Assuming this, our analysis suggests that adopting a more aggressive screening strategy in higher-risk persons (i.e., every 5 years from age 40) while maintaining the current strategy for those without a family history shows reasonable value, although at a higher cost than current screening recommendations.

We used simple variations in screening rates because these are more feasible for adoption. It is theoretically possible to find ideal screening rates based on polyp behavior in high- and low-risk persons, but the intervals may not be intuitive or easy to remember for clinicians or the public.

CRC screening rates are suboptimal among eligible persons, although rates have been improving somewhat over the last several years.[44] In addition, questions have been raised about the overall availability of colonoscopy for screening relative to demand,[45] and the possibility of endoscopy overuse in some groups compared with recommendations, particularly among persons who have had adenomas identified before screening exams.[46] Given limited endoscopy capacity and budget, FHS may increase use among those who would benefit most from more screening while at the same time reducing the intensity of screening among those who have less to gain.

There are several uncertainties that should be considered and possibly studied formally before or during the implementation of new screening policies based on family history. It is not known whether persons at higher risk by virtue of family history are more likely to adhere to more intensive screening programs. Polyp behavior in those with family histories is still not well characterized, particularly the rate of transformation from adenoma to invasive cancer. Prospective, controlled trials have not been conducted to gauge the costs and effectiveness of colonoscopy in general populations, let alone for stratified populations. The recommendations for FHS vary somewhat amongst expert groups, further adding to the uncertainty regarding optimal screening schedules. As the data are not known, we do not know how variations between the family history definitions in guidelines would change the proportion of the population who would be considered to have a positive-family history. In the future, genetic testing for variants

may confer more precise estimates of lifetime CRC risk than those currently available from FHS, permitting tailored screening schedules.

FHS may be somewhat less cost-effective if FHS adversely affected quality of life for those found to be at higher risk, although presumably most persons with affected relatives have already adjusted to this information and its implications for their own personal risk. These issues will affect the cost-effectiveness of proposed strategies for implementing family history-based screening strategies for CRC.

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8

How much colonoscopy screening should be recommended to individuals with various degrees of family history of colorectal cancer?

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ABSTRACT

Background: Individuals with a family history of colorectal cancer (CRC) are at increased risk for CRC. Current screening recommendations for these individuals are based on expert opinion. The authors investigated optimal screening strategies for individuals with various degrees of family history of CRC based on a cost-effectiveness analysis.
Methods: The MISCAN-Colon microsimulation model was used to estimate costs and effects of CRC screening strategies, varying by the age at which screening was started and stopped and by screening interval. The authors defined 4 risk groups, characterized by the number of affected first-degree relatives and their age at CRC diagnosis. For all risk groups, the optimal screening strategy had an incremental cost-effectiveness ratio of approximately $50,000 per life-year gained.
Results: The optimal screening strategy for individuals with 1 first-degree relative diagnosed after age 50 years was 6 colonoscopies every 5 years starting at age 50 years, compared with 4 colonoscopies every 7 years starting at age 50 years for average risk individuals. The optimal strategy had 10 colonoscopies every 4 years for individuals with 1 first-degree relative diagnosed before age 50 years, 13 colonoscopies every 3 years for individuals with 2 or more first-degree relatives diagnosed after age 50 years, and 15 colonoscopies every 3 years for individuals with 2 or more first-degree relatives of whom at least 1 was diagnosed before age 50 years.
Conclusions: The optimal screening strategy varies considerably with the number of affected first-degree relatives and their age of diagnosis. Shorter screening intervals than the currently recommended 5 years may be appropriate for the highest risk individuals.

Introduction

Individuals with a family history of sporadic colorectal cancer (CRC) are at increased risk for the disease.[1-3] Approximately 11% of the population aged 30 to 70 years has at least 1 first-degree relative diagnosed with CRC.[4,5] Of all CRC cases, 2% to 5% occur in individuals with known genetic disorders such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC).[6] Without treatment, the lifetime CRC risk is >95% in individuals with FAP, and 50% to 80% in individuals with HNPCC.[6] Our focus, however, is on individuals with at least 1 affected first-degree relative and no known genetic disorders, accounting for another 25% of all CRC cases. These individuals have approximately a 2-fold increased risk compared with the average risk population. The individual risk level increases with an increasing number of affected first-degree relatives and a younger age of diagnosis of the affected relatives.[2] We consider 4 risk groups of individuals with a CRC family history (excluding known genetic disorders), with a varying relative risk (RR): (1) 1.6 for individuals with 1 first-degree relative diagnosed after age 50 years, (2) 2.6 for individuals with 1 first-degree relative diagnosed before age 50 years, (3) 3.5 for individuals with 2 first-degree relatives both diagnosed after age 50 years, and (4) 5.6 for individuals with 2 first-degree relatives with at least 1 diagnosed before age 50 years.

Colonoscopy with removal of adenomas, the noninvasive precursor of CRC, decreases CRC incidence in both average risk individuals and in subjects with hereditary CRC syndromes.[7,8] Although it is generally advised that individuals with a family history of CRC have more intensive screening than the average risk individuals, the optimal strategy remains unclear. Expert opinion-based recommendations include a start of colonoscopy screening 10 years earlier in individuals with a family history than in the average risk population, or 10 years before the youngest age of diagnosis of the affected relatives.[9-11] Another recommendation is to use a 5-year interval for individuals with 1 first-degree relative diagnosed before age 60 years or 2 or more first-degree relatives diagnosed at any age, instead of the 10-year interval for the average risk population.[12-14] The differentiation in current guidelines for the 4 risk groups defined above is minor, whereas the risk levels increase considerably, suggesting that more differentiation is needed.

We will identify the optimal screening strategies per risk group based on a cost-effectiveness analysis. We hereto used the MISCAN-Colon simulation model and the results from a recent meta-analysis.[2]

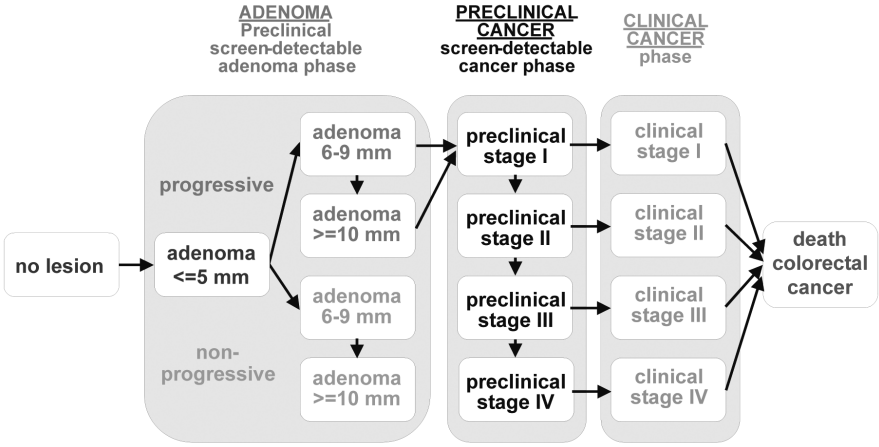

Figure 8-1. Adenoma and cancer stages in the MISCAN-Colon model are shown. Cancer stages correspond to the American Joint Committee on Cancer/International Union Against Cancer staging system for colorectal cancer. Adenomas are categorized by size.

MATERIALS AND METHODS

MISCAN-Colon

The MISCAN-Colon microsimulation model was developed at the Department of Public Health at Erasmus MC, the Netherlands, in collaboration with the US National Cancer Institute to assess the effect of different interventions on the occurrence of CRC in a population. A detailed description of the model and the data sources that informed the quantification of the model can be found in previous publications[15,16] and also in a standardized model profiler.[17] In brief, the model simulates individuals from birth to death, first without screening and subsequently with the changes that would occur under the implementation of a screening program. In every individual, adenomas can arise, and some of them will develop into cancer. A schematic representation of the natural history as used in the model is given in Figure 8-1. Adenomas are initially small (1-5 mm) and progress to medium (6-9 mm) and large (10+ mm) adenomas. The majority of adenomas are assumed to be nonprogressive and will never develop into cancer. The progressive adenomas have the ability to become cancer, but not all of them will make it to cancer in an individual's lifetime. The adenomas that do become malignant transform into stage I cancers and will progress into stages II, III, and IV, unless diagnosed earlier. The survival after clinical diagnosis depends on age and the cancer stage at diagnosis. Screening can result in a gain in life-years when cancers are detected and treated at earlier stages or when adenomas are detected and consequently removed before they become cancer.

The validity of the model has been tested on the results of large (randomized) screening and surveillance studies. In particular, we were able to simulate the same number of screen-detected and interval cancers as observed in the Minnesota Colon Cancer Control Study, the Funen trial and the Nottingham trial,[18] the CoCap sigmoidoscopy study,[19] and the National Polyp Study.[20] The model was able to explain observed incidence and mortality trends in the United States when accounting for risk factor trends, screening practice, and chemotherapy treatment.[21]

For the average risk population of this analysis, disease parameters were adjusted to reproduce adenoma prevalence data from autopsy studies[22-31] and Surveillance, Epidemiology, and End Results (SEER) incidence data from 1975 to 1979,[32] when they were not yet influenced by screening. Survival after CRC diagnosis by stage was based on SEER 1996 to 1999 data.[32]

Population and Risk Levels

We modeled a cohort of 30-year-olds in the United States in 2005. We categorized the individuals with a family history into 4 risk groups, depending on the number of first-degree relatives or age at diagnosis. The RR estimates per group were based on a recent meta-analysis.[2] The groups consisted of (1) individuals with 1 first-degree relative diagnosed after age 50 years, with a RR of 1.6; (2) 1 first-degree relative diagnosed at or before age 50 years (RR, 2.6); (3) 2 or more first-degree relatives diagnosed after age 50 years (RR, 3.5); and (4) 2 or more first-degree relatives with at least 1 of them diagnosed at or before age 50 years (RR, 5.6). These 4 groups are shortly referred to as ''1 first-degree relative >50 years,'' ''1 first-degree relative ≤50 years,'' ''2+ first-degree relatives >50 years,'' and ''2+ first-degree relatives ≤50 years.'' Individuals with a family history were simulated by adjusting the RR for CRC compared with the average risk population. We modeled the increased risk for CRC by multiplying the age-specific adenoma onset rate for both progressive and nonprogressive adenomas by the same RR for all ages.

Screening Strategies

For every risk group we simulated colonoscopy screening strategies, which differed with respect to:

- The age at which screening was started, which varied between 30 and 60 years;
- The screening interval that varied between 2 and 10 years;
- The age at which screening was stopped, which was never after the age of 90 years; and
- The number of colonoscopies followed from the previous 3 parameters, which had to be at least 2.

Individuals with adenomas were referred to surveillance following the guidelines

of the US Multi-Society Task Force on Colorectal Cancer.[33] If the screening interval was shorter than the recommended surveillance interval, the latter was shortened to the screening interval.

Per polyp sensitivity was assumed to be the same for screening and surveillance colonoscopy: 80% for small adenomas, 85% for medium adenomas, and 95% for large adenomas and cancers.[34-36] We assumed complications like perforations and bleedings to occur at a rate of 2.4 per 1000 colonoscopies.[37-40] Colonoscopy with polypectomy resulted in mortality once in every 10,000 colonoscopies.[41] We assumed a 100% compliance for both screening and surveillance colonoscopies. In this way, our analyses focus on optimal strategies for individuals who comply with the guidelines.

Costs

Costs included costs for colonoscopy, complications of colonoscopy, and treatment of CRC (Table 8-1). The costs of colonoscopy screening and surveillance were assumed to be equal, but to depend on whether polypectomy was performed. The costs associated with colonoscopy were based on 2007 Medicare average payments.[42] Costs for complications of colonoscopy were based on the relevant diagnosis-related group codes.[42] Treatment costs were derived from a comparison of costs for CRC cases relative to matched controls in the SEER-Medicare files.[43] All costs were updated to 2007 dollars using the medical care component of the Consumer Price Index. The final cost inputs used in the model are summarized in Table 8-1.

Analysis

We used the MISCAN-Colon model to estimate costs and number of life-years gained compared with the situation without screening for all screening strategies. For each risk group, we identified the efficient screening strategies, that is, strategies that did not have an alternative or combination of alternatives that would result in more life-years at the same or less costs. This resulted in a set of efficient strategies for each risk group. For every efficient strategy, we determined the incremental cost-effectiveness ratio (ICER), which is calculated as the incremental costs per incremental life-year gained compared with the next less cost-efficient strategy. For all risk groups, the optimal strategy was considered the strategy with an ICER value closest to a threshold of $50,000 per life-year gained.[44] Costs and life-years gained were discounted at 3% per year.

Sensitivity Analysis

There is uncertainty on the dwell time of adenomas. Recent data from a randomized controlled sigmoidoscopy study have indicated a probably longer dwell time than the

Table 8-1. Assumptions for Costs (2,007 Dollars) and Complications Associated With Colonoscopy and Colorectal Cancer Treatment[43]

Polypectomy				*Colonoscopy costs*
Without				$662
With				$846
Colonoscopy complications[a] *(with and without polypectomy)*	*Rate per 1000 Colonoscopies*			*Costs*
Perforations	0.7			$12,446
Serosal burn	0.3			$5,208
Bleed with transfusion	0.4			$5,208
Bleed without transfusion	1.0			$320
	Treatment costs per phase of care[b]			
Stage at diagnosis	*Initial*	*Continuous (per year)*	*Terminal care (death from CRC)*	*Terminal care (death from other cause)*
Stage I	$28,668	$2,395	$51,935	$12,703
Stage II	$39,700	$2,237	$51,712	$11,035
Stage III	$48,951	$3,249	$54,776	$14,708
Stage IV	$64,801	$10,419	$73,522	$39,679

CRC indicates colorectal cancer.

[a] Once in every 10,000 colonoscopies with polypectomy the complication is assumed to be fatal.

[b] Costs for cancer care were divided into 3 clinically relevant phases of care—initial, continuing, and terminal care. The initial phase was defined as the first 12 months after diagnosis, the terminal phase was defined as the final 12 months of life, and the continuing phase was defined as all months between the initial and terminal phases. For patients surviving <24 months, the final 12 months were allocated to the terminal phase. The remaining months of observation were allocated to the initial phase.

20 years we assumed, at least for distal lesions.[45] Therefore, we repeated the analysis with an increased mean dwell time of 30 years for the average population. The adenoma incidence by age was concurrently adjusted to keep the CRC incidence unchanged. To account for the influence of screening and CRC treatment on quality of life, we used quality-adjusted life-years as a sensitivity analysis. We assumed 1 day loss per colonoscopy, and a loss of 0.26, 0.3, 0.4, or 0.75 per year in stage I, II, III, or IV initial care, a 0.15 loss per year in continuous care, a 0.75 loss per year in terminal care before dying of CRC, and a 0.35 loss per year in terminal care in the case of dying of another cause.[46,47] We assessed the influence of discounting by repeating the analysis with a discount percentage of 0% and 5%.

For the highest risk group, we performed a sensitivity analysis on the way the disease develops by modeling the increased risk with a shorter adenoma dwell time of 10 instead of 20 years.

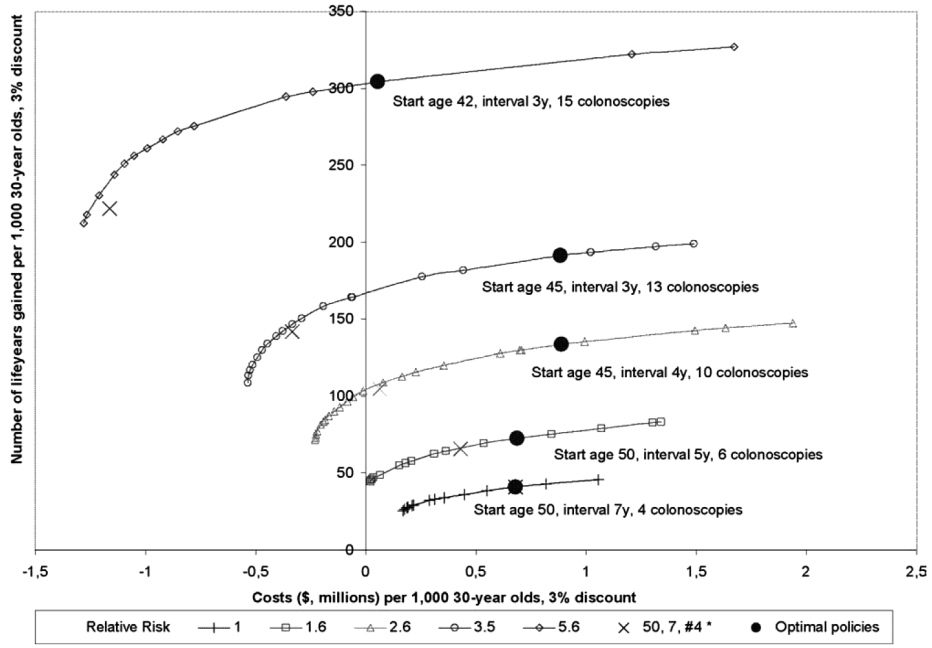

Figure 8-2. Discounted costs (millions of dollars) and life-years gained per 1000 30-year-olds of the efficient strategies are shown, with relative risk levels corresponding to the category of family history.

We decided not to perform a probabilistic sensitivity analysis after having weighed the computational effort required against the limited added value because of the lack of data on the probability distributions of most of the parameter values.

RESULTS

The efficient strategies per risk group are shown in Figure 8-2. The higher the risk among those screened, the more life-years were gained at the same costs. Because of the greater health gain in higher risk groups, more intensive strategies, with shorter screening intervals and wider age ranges, met the criteria of an ICER close to $50,000 per life-year gained (Table 8-2). For individuals with 1 first-degree relative >50 years, the optimal strategy had an interval of 5 years. The optimal age to start screening in this group was 50 years, and the optimal age to stop screening was 75 years. For individuals with 1 first-degree relative ≤ 50 years, the optimal screening interval was 4 years, and the optimal ages to start and stop screening

were 45 and 81 years. The optimal screening interval for individuals with 2+ first-degree relatives >50 years was 3 years, with the same age range (45-81 years). For individuals with 2+ first-degree relatives ≤ 50 years, the optimal screening interval was also 3 years, with a further widened age range of 42 to 84 years. The mortality reduction that resulted from the optimal strategies varied between 72% and 84%, and increased with risk level. The number needed to scope to prevent 1 death decreased from 220 for individuals with 1 first-degree relative >50 years to 130 for individuals with 2+ first-degree relatives ≤ 50 years.

For the average risk population, the optimal screening strategy had an interval of 7 years, starting at age 50 years and stopping at age 71 years (4 colonoscopies). Therefore, according to our model, if one has the resources to screen the general population 4x, it would be more cost-effective to screen those aged from 50 to 71 years every 7 years than to screen, for example, those aged from 50 to 80 years every 10 years. Only if one has no more resources than needed to provide 2 colonoscopies in a lifetime would one screen every 10 years.

Sensitivity Analysis

With an adenoma dwell time of 30 instead of 20 years, the strategy with 3 instead of 4 colonoscopies every 7 years starting at age 50 years had an ICER closest to $50,000 per life-year gained for the average risk population, because of an increased ICER value of both strategies. Adjusting for quality of life resulted in more quality-adjusted life-years than nonadjusted life-years because of the prevention of CRC by colonoscopy screening and a consequently lower number of life-years in treatment. The incremental effectiveness conversely decreased with an increasing number of colonoscopies because of the 1day loss per colonoscopy. At a threshold of $50,000 per quality-adjusted life-year, the optimal strategy for individuals with 1 first-degree relative >50 years changed to screening every 4 instead of every 5 years between the ages of 50 and 74 years. The strategies for the higher risk groups remained the same. Discounting had a more substantial impact on the effects of screening and savings from treatment than on colonoscopy costs, because the latter occur earlier in time. As a consequence, not discounting was favorable for screening, with shorter intervals and more colonoscopies as a result (Table 8-3). With a 5% discount, in contrast, we found longer screening intervals and fewer colonoscopies. With a shorter adenoma dwell time for individuals in the highest risk group, the optimal screening interval was 2 instead of 3 years, with screening ages between 44 and 88 years.

Table 8-2. Optimal screening strategies at various relative risk levels associated with a family history of colorectal cancer, and their associated costs (in dollars) and life-years gained per 1000 30-year-olds.

		Optimal strategy			Compared to no screening, per 1,000 30-year-olds				Compared to next less expensive efficient strategy
Category of family history	Relative risk	No. of screens	Screening interval, y	Age range, y	Mortality reduction, %	No. needed to scope to prevent 1 death	Total costs	No. of life-years gained	ICER
1 FDR diagnosed after age 50 years	1.6	6	5	50-75	72	220	$690,000	72	$48,000
1 FDR diagnosed before age 50 years	2.6	10	4	45-81	79	190	$890,000	134	$50,000
2 or more FDRs diagnosed after age 50 years	3.5	13	3	45-81	84	180	$880,000	191	$47,000
2 or more FDRs, at least 1 diagnosed before age 50 years	5.6	15	3	42-84	84	130	$50,000	304	$46,000

ICER indicates incremental cost-effectiveness ratio; FDR, first-degree relative.
Discount of costs and effects is 3% yearly.

Table 8-3. Optimal strategies per relative risk level for the sensitivity analysis on discounting, 0% and 5%[2]

		Optimal strategy, 0% discount			Optimal strategy, 5% discount		
Category of family history	Relative risk	No. of screens	Screening interval, y	Age range, y	No. of screens	Screening interval, y	Age range, y
1 FDR diagnosed after age 50 years	1.6	9	4	45-77	6	6	49-79
1 FDR diagnosed before age 50 years	2.6	14	3	42-81	10	4	47-83
2 or more FDRs diagnosed after age 50 years	3.5	15	3	41-83	11	4	44-84
2 or more FDRs, at least 1 diagnosed before age 50 years	5.6	23	2	41-85	15	3	43-85

FDR indicates first-degree relative.

Discussion

The optimal colonoscopy screening strategy for individuals with a CRC family history had a screening interval of 3 to 5 years, depending on the number of affected relatives and their age at diagnosis. The age ranges of the optimal strategies varied from 50-75 to 42-84.

Sometimes higher thresholds than $50,000 per life-year gained are considered acceptable,[44] allowing more frequent colonoscopy screening. Increasing the threshold up to $75,000 resulted in screening intervals of 2 to 4 years and age ranges that varied from 46-78 to 43-89 (results not shown). Further increasing the threshold to $100,000 did not shorten the intervals further, but only resulted in 1 or 2 additional colonoscopies in the 2 highest risk groups.

Screening becomes somewhat less cost-effective in individuals without affected relatives, because they have a lower risk than the total population (RR, 0.9). To adjust to the threshold ICER used, theoretically screening intensity needs to be decreased slightly.

There are several US guidelines for CRC screening in individuals with a family history.[11,12,14] In some guidelines, screening starts at age 40 years if someone has at least 1 affected first-degree relative. In the case of 1 first-degree relative diagnosed after age 60 years, the recommended screening interval is 10 years, as in the general population. For individuals with 1 first-degree relative diagnosed before age 60 years and for individuals with 2 or more first-degree relatives, 5-yearly colonoscopy is recommended. Others have suggested, based on prospective observational studies, that screening should start at age 45 to 50 years, and that colonoscopy every 5 years would be sufficient.[48,49] Controlled studies to analyze the effect of these strategies on incidence or mortality are not available. Our results are in line with a recommended starting age of 45 years, but with shorter intervals. However, note that the shorter intervals for individuals with 1 first-degree relative ≤50 years or 2+ first-degree relatives were approximately half the interval for the average risk population (3-4 *vs* 7 years according to our results), which corresponds with the 50% difference in interval as recommended in the guidelines (5 *vs* 10 years). The 10-yearly recommendation for the average risk population was based on expert opinion, and chosen for simplicity. This strategy was suboptimal in our analysis, because it was as effective as 3 colonoscopies every 7 years starting at age 54 years, but more expensive ($0.50 instead of $0.45 million). This strategy with a 7-year interval had an ICER of $43.000 per life-year gained, which is close to the threshold of $50,000 per life-year gained.

Lengthening the model assumption of the average dwell time for an adenoma to become cancer from 20 to 30 years did not lengthen our optimal screening interval for

the average risk population. However, as expected, the incremental cost-effectiveness of 4 colonoscopies relative to 3 colonoscopies became worse because of the lower incremental effectiveness of the last colonoscopy. By lengthening the dwell time further, the ICER of 3 colonoscopies every 7 years would eventually increase to >$50,000 per life-year gained as well, and longer intervals would become optimal in combination with fewer screening rounds. Besides a longer adenoma dwell time, higher colonoscopy costs relative to the treatment costs would also challenge our conclusion that shorter screening intervals may be appropriate than currently recommended. However, this is unlikely in view of the increasing costs of chemotherapy drugs involved in CRC treatment. We looked at the influence of trends in survival and treatment costs in an earlier analysis, where more recent survival data, taking the effects of greater use of adjuvant treatment into account, had a minimal effect on the number of life-years gained.[50] This will therefore have a small impact on our results. Another important assumption is that increased cancer risk is caused by an equally increased adenoma incidence across all ages. We assessed this assumption in an earlier analysis based on several colonoscopy studies.[51] Alternatively, a faster progressive development of adenomas could cause higher risk in these individuals. We found a shorter interval of 2 instead of 3 years for the highest risk group when we assumed the increased risk to be caused by a combination of a higher adenoma incidence and faster progression of the adenomas. Therefore, this would suggest even more diversification in screening intensity between risk groups.

A limitation of this study is that we did not account for the number of first-degree relatives an individual has, which affects the risk for CRC. For example, an individual with 2 first-degree relatives both diagnosed with CRC is at higher risk than someone with 10 first-degree relatives, 2 of whom are diagnosed with CRC. Also family history, and thus the estimated risk of an individual, changes over time, because relatives are or are not being diagnosed with CRC. Ideally, the screening strategy is adjusted accordingly.

Our results show that individualizing screening guidelines based on family history could improve the effectiveness substantially. Individualized guidelines are more complex than the current guidelines and could confuse both physicians and screenees, resulting in lower adherence rates. Individuals could also hesitate to adhere to more frequent invasive colonoscopies, especially if their insurance company does not cover earlier or more frequent colonoscopies. Adherence generally does not influence the cost-effectiveness of screening, because it influences both costs and effects, and was therefore assumed to be 100% in our analysis. However, lower adherence rates would obviously decrease the effectiveness of screening. Conversely, individualized guide-

lines could also increase the adherence because of a better awareness of the individuals risk for CRC. Besides, it fits with the trend toward more personalized medical care, and individuals might appreciate that the recommendation is based on their personal risk profile. Implementation studies should look into these issues.

Risk for CRC also depends on lifestyle. Recently, a risk prediction tool has become available that estimates an individual's CRC risk based on a self-administered questionnaire.[52,53] Both family history and lifestyle factors are included. Results of cost-effectiveness analyses, such as those presented in this article, can be used to translate the risk estimates resulting from this prediction model to screening recommendations.

In conclusion, the optimal colonoscopy screening strategy varies considerably with the number of affected relatives and their age of diagnosis. For the higher risk individuals, shorter intervals than the currently recommended 5 years may be appropriate.

CONFLICT OF INTEREST DISCLOSURES

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9

General discussion

Discussion

In this thesis, we have assessed the health effects and costs of colorectal cancer (CRC) screening in the general population, and in individuals with a family history of the disease. We formulated research questions on stool testing for the general population, and on colonoscopy screening for individuals with a colorectal cancer family history. In this chapter, we will answer these research questions. Next, we will discuss directions for future research. We will end the thesis with conclusions and recommendations.

Answers to the research questions

How do attendance rates and test characteristics of guaiac and immunochemical fecal occult blood testing for colorectal cancer compare?

Screening with fecal immunochemical test (FIT) was better attended than screening with the guaiac fecal occult blood test (gFOBT). FIT has also better test characteristics than gFOBT.

Only gFOBT has been proven to reduce colorectal cancer mortality in randomized controlled trials.[1-3] FIT has been introduced more recently, and has some important advantages over gFOBT. One of the advantages is that FIT detects specifically human blood, while gFOBT cannot distinguish human blood from consumed animal blood. This implicates that with FIT screening, there is no need for dietary restrictions. Also, with a quantitative FIT one can choose the cutoff level for referral to colonoscopy. Finally, the analysis of FIT is largely automated, which reduces handling time and makes quality control easier. But the most crucial issues for comparison of the two tests are attendance and test properties.

In our studies, the attendance to FIT screening was 12% higher than to gFOBT (62% versus 50%). The difference was not caused by dietary restrictions for gFOBT, because no such restrictions were made. The difference in sampling methods, including the larger number of stool samples needed for gFOBT, seems a likely explanation for the difference in attendance.

As to test characteristics, several studies have shown that they are better for FIT than for gFOBT.[4,5] Our study confirmed this in a randomized setting. At a cutoff level of 200 ng hemoglobin/ml, a higher detection rate for advanced neoplasia was found for FIT than for gFOBT, while the specificity was similar. With a decreasing FIT cutoff level, both true and false positive rates increase. At a 75 ng/ml cutoff, the number of colonos-

copies needed to detect one advanced neoplasia was similar for FIT and gFOBT, but FIT detected more than twice as many cases of advanced neoplasia.

Altogether FIT seems a better test than gFOBT. Whether the FIT test should be used in an organized screening program (and if so, with what cutoff level) does not only depend on attendance and test characteristics, but also on background risk, on colonoscopy capacity, on the burden associated with screening and with positive test results, and on costs.

What is, in a colorectal cancer screening program with a fecal immunochemical test, the appropriate cutoff level for referral to colonoscopy and what are the optimal screening ages?

The lowest 50 ng hemoglobin/ml cutoff level for referral to colonoscopy of the fecal immunochemical test (FIT) evaluated is preferred over higher cutoff levels. Starting screening between ages 50 and 55 and stopping between ages 75 and 80 is a good option.

According to the manufacturer, the recommended cutoff level for referral to diagnostic colonoscopy for the immunochemical OC-Sensor is 100 ng/ml. We found that a lower cutoff level of 50 ng/ml, with a better sensitivity and a lower specificity, is more cost-effective. Due to the high treatment costs for CRC, the costs of the additional colonoscopies are outweighed by the increased savings from less clinical cancer treatment. Some studies came to different conclusions, but this can be explained by the fact that they used different optimality criteria (see also Chapter 3).[6-10]

In the EU, US and Canada, individuals between ages 50 and 75 are recommended to be screened for CRC. Our results confirm that this is a reasonable age interval. Starting 5 years later or stopping 5 years later were good alternatives. Within these age ranges, screening every 2 years had an ICER of 3,900 euro per life-year gained. In many countries, the implementation of a biennial screening program in such a broad age range causes practical problems because of a limited colonoscopy capacity. Annual screening is therefore often not even considered. From a cost-effectiveness point of view, annual screening could also be recommended.

In our analysis, the age to stop screening was based on the average life expectancy of the general population. However, on an individual level the optimal age to stop screening also depends on co-morbidity. Individuals in poor health have a short life expectancy and are therefore less likely to benefit from screening. Also, they sometimes are more likely to suffer from complications of colonoscopy.

In current FOBT screening programmes gFOBT is often used, because of its proven effectiveness and cost-effectiveness, and because it induces a low colonoscopy demand. With the advent of FIT, several countries consider changing to FIT because of its higher attendance and better test characteristics. Changing from gFOBT to FIT with a 100ng/ml cutoff has been estimated to cost 3,000 euro per additional life-year gained,[11] and is therefore cost-effective. Our results show an even more favourable incremental cost of 1,000 euro per life-year gained when a change is made to FIT with a 50 ng/ml cutoff (in combination with biennial screening between ages 55-75). In the US, one of the recommended FOB-tests is the Hemoccult Sensa. Hemccult Sensa is also guaiac-based but with different test characteristics than the Hemoccult II that was used in the randomized controlled trials on mortality reduction, and considered in our analysis. One study found a comparable sensitivity of Hemoccult Sensa and FIT, but with a much lower specificity for Hemoccult Sensa.[4] Hemoccult Sensa is recommended in the US because the reimbursement rate is higher for FIT than for gFOBT ($22 for FIT compared to $4.50 for either gFOBT). Based on the Dutch trial, costs for FIT did not turn out to be much higher than for gFOBT,[12] and therefore FIT is to be preferred over Hemoccult Sensa.

How should screening with a fecal occult blood test be adjusted in order to deal with a limited colonoscopy capacity?

Increasing the cutoff level for referral to colonoscopy is the principal way to limit colonoscopy demand of fecal immunochemical test (FIT) screening. In addition, less intensive surveillance after polypectomy and less screening rounds can be considered, depending on the actual capacity.

The decision on whether or not to start with fecal occult blood testing (FOBT) should not depend on the colonoscopy capacity because CRC screening is cost-effective at all capacity levels. The screening program should however be adapted to the available colonoscopy capacity, as indeed has been done in several countries. Colonoscopy demand can be limited by using the highly specific Hemoccult II test, by using FIT with a high cutoff level for referral to colonoscopy, by screening less frequently or in a smaller age range, or by reducing the intensity of post polypectomy surveillance colonoscopy. Finland and the UK introduced screening with the Hemoccult II starting with a small age range of 60-69. Not one country started with FIT at a high cutoff level, which would have been the best approach in reducing colonoscopy demand when considering health benefits and cost-effectiveness.

In case of increasing colonoscopy capacity over time, intensification of an ongoing colorectal cancer screening program should be considered. Lowering the FIT cutoff level can take place without practical changes for the invited population. The possible consequences of screening and the likelihood of their occurrence should however be communicated at invitation, and these change when the cutoff levels change. Changes in the ages at which individuals are invited and changes in the surveillance schedules after polypectomy require adaptations in guidelines and registration, and should be communicated carefully, in order to avoid confusion.

The use of high cutoff levels for FIT is the preferred approach to reduce colonoscopy demand because it will result in the highest health benefit. This approach avoids the follow up of individuals with relatively low hemoglobin levels in their stool, which generates many colonoscopies for few detected lesions, because individuals with low hemoglobin levels are at considerably lower risk than individuals with higher levels. Limiting colonoscopy demand through one of the other approaches is less beneficial because more advanced disease will be missed.

How do attendance and test characteristics of 2-sample screening from different stools with a fecal immunochemical test compare with those of 1-sample screening?

Attendance to 1- and 2-sample screening with a fecal immunochemical test (FIT) is similar. Using 2 samples provides the possibility to choose over a wide range of combinations of detection and positivity rates, depending on the definition of a positive combined test result. This gives enhanced flexibility in adjusting to the colonoscopy capacity.

The test results of the two samples can be combined in different ways. By referring everyone with at least one positive sample to colonoscopy, the use of two FIT samples increases the probability that an intermittently bleeding lesion is detected. However, it also increases the number of false positive test results. At a 50 ng/ml hemoglobin cutoff level for referral to colonoscopy, the proportion of individuals with at least one positive test was over 50% higher than the proportion of individuals with a positive test with a one sample FIT (12.8% versus 8.1%). This resulted in a 30% increase of advanced neoplasia detected (4.1% versus 3.1%).

Thus, the diagnostic yield of two samples is higher, and the positive predictive value (PPV) lower than for screening with one sample. If, on the contrary, only those individuals with two positive test results are referred to colonoscopy, the diagnostic yield will be lower, and the PPV higher than with one sample. Thus, variable use of the results

of two samples gives more flexibility in adjusting to the available colonoscopy capacity than can be obtained by varying the FIT cutoff level alone.

The performance of a screening program depends on the attendance rates. Shorter screening intervals might lower attendance rates. Using two samples with a longer screening interval could therefore be a good alternative to one sample screening with a shorter interval. This is also interesting from a cost perspective since offering individuals two samples at the same time is less expensive than inviting individuals twice. On the other hand, one would expect extra yield when lengthening the interval to one or two years instead of one or more days. Data on attendance rates and diagnostic yield at varying screening intervals are expected from the Dutch trials in the near future and can be used for a more informed comparison of using 2-sample FIT screening with longer intervals and 1-sample with shorter intervals.

Are individuals with a family history of colorectal cancer at increased risk for developing colorectal adenomas, besides their increased risk for cancer?

Individuals with a family history of colorectal cancer (CRC) are at increased risk for colorectal adenomas, which largely explains their risk for cancer.

Approximately 2-5% of all CRC is caused by a known genetic disorder. Another 25% develops in individuals with a family history for CRC, but without a known genetic disorder. These individuals have on average approximately a twofold lifetime CRC risk compared to the general population. About 10% of the population aged between 30 and 70 has at least 1 first degree relative with CRC. A study on twins suggested that about 35% of all CRC cases can be attributed to heritable factors.[13] Given that only 5% of all CRC cases are caused by known genetic syndromes like FAP and HNPCC, genetic factors must also be involved in the other, so called sporadic CRC. This is confirmed by a study that found an associated risk among siblings and between parents and offspring, but no association between spouses that had lived together for at least 30 years.[14] The associated risk among siblings was especially high for proximal cancers.

Individuals with a family history of colorectal cancer (CRC) are at increased risk for harbouring any colorectal adenoma. It is reasonable to expect that individuals with an increased risk for having any adenomas, also develop more adenomas on average, and this has indeed been observed.[15] In addition, a somewhat more aggressive development of adenomas in individuals with a family history remains a possibility. But because of

the higher adenoma prevalence, a more aggressive development is not necessary to explain the higher risk for CRC. Because we were interested in age trends, we only included studies with observations in more than one age interval in our analysis. Studies with only one age interval supported the conclusion that individuals with a CRC family history have an increased risk for adenomas.[16-19] One study found indications for a faster development of adenomas, by not removing small adenomas, estimating their growth at a colonoscopy one year later and comparing this with individuals without a CRC family history.[20]

The question whether increased risk of CRC is due to more adenoma incidence or to more rapid development of adenomas is relevant because of its implications for screening. With an increased adenoma prevalence (as a result of higher incidence) it is easier to prevent individuals from developing CRC than with a faster development of the disease, since slow growing adenomas are easier to detect by periodic screening.

What are optimal colonoscopy screening policies for individuals with varying family histories of colorectal cancer?

Individuals with a family history for colorectal cancer (CRC) should be screened with about half the interval used for average risk individuals, depending on the number of affected first degree relatives and the age of these relatives at their diagnosis.

In many countries, individuals with a family history that are tested negative for a genetic disorder, and also individuals with only a moderate family history are referred to colonoscopy. The recommended colonoscopy frequency differs between countries. In the Netherlands, individuals come back every six years as long as no more than 2 adenomas are found. In the United Stated, the interval is 5-10 years. Active recruitment of individuals with a family history (at a cost of $35 per individual), and offering these individuals 5-yearly instead of 10-yearly colonoscopy, costs approximately $50,000 per life-year gained (Chapter 7). The costs for recruiting these individuals could be reduced if performed systematically as part of a population-based invitational screening program, in which every individual could be asked for his or her family history in the first round, and for updates in later rounds.

The guidelines mentioned above are based on expert opinion rather than on evidence. We therefore simulated strategies over a much wider range of screening ages and intervals (Chapter 8). We found that when using half the screening interval of the general population, screening individuals with a family history was approximately as

cost-effective as screening the general population with the longer interval. At an incremental cost-effectiveness ratio of $50,000 per life-year gained, the optimal strategy for the general population was screening every 7 years between age 50-71. Due to the associated variation in excess risk, the optimal strategy varied with the number of affected first degree relatives and their age at diagnosis:

- every 5 years between ages 50-75 for individuals with 1 first degree relative (FDR) diagnosed after age 50,
- every 4 years between ages 45-81 for individuals with 1 FDR diagnosed before age 50
- every 3 years between ages 45-81 for individuals with 2 FDRs diagnosed after age 50
- every 3 years between ages 42-84 for individuals with 2 FDRs if at least one is diagnosed before age 50

When individuals with a family history are offered a more intensive screening program, on average lower risk individuals remain in the screening program. As a consequence, the cost-effectiveness of the screening program will become slightly worse.

The above mentioned results have been derived under the assumption that the increased CRC risk was caused by an increased risk for developing adenomas. When also assuming a more aggressive development of the disease in persons with a family history, even shorter screening intervals would be recommended. Whether individuals will comply to the same extent with shorter as with longer screening intervals is uncertain. Colonoscopy is an invasive test with a risk for serious complications. There is very few data on the impact of colonoscopy screening on quality of life. There has been one study estimating quality of life 30 days before and after colonoscopy, which found that mental health and vitality domains of quality of life significantly improved after colonoscopy. The burden in the period closer to the colonoscopy was not assessed. The experienced burden could have a negative effect on attendance rates if screening intervals are shortened, which would decrease the effectiveness of these strategies.

In the absence of randomized controlled trials, the effectiveness of colonoscopy is uncertain. Case control studies suggest a limited effectiveness of colonoscopy in the proximal colon.[21,22] Also the proximal CRC incidence in individuals receiving colonoscopy after a positive flexible sigmoidoscopy was hardly reduced. In the distal colon on the contrary, the effectiveness of endoscopy was found to be substantial.[23,24] In individuals with a family history, CRC tends to arise more frequently in the proximal colon.[25, 26] In our analysis, we assumed colonoscopy to be equally effective in the proximal and distal colon (as long as within its reach), which may have been a bit too optimistic.

FUTURE RESEARCH

Validation against data from continued FIT screening

There is sufficient evidence to support the start of population based screening programs with FIT. FIT is to be preferred over gFOBT because of its higher attendance rate (at least in the Netherlands), better test characteristics and similar costs. For FIT, the data used in the cost-effectiveness analysis in this thesis came from the first screening round of recent Dutch trials. The simulation results should be validated against the attendance, positivity and detection rates of later screening rounds. The Dutch trials are very informative for later rounds, because they have arms with different screening intervals. Repeated screening will provide more information on bleeding patterns of prevalent lesions, the development of new lesions, and on the number of individuals with a systematic false positive test result. There are as yet limited data on follow up rounds of population based FIT screening.

After nationwide implementation of colorectal cancer screening in the Netherlands, trial results and expectations build on these results should be compared with national data (attendance and findings in first and subsequent rounds and costs). Strong evidence on the effectiveness of FIT will eventually come from data on interval cancers, and from the age specific colorectal cancer mortality trend in the total population.

Comparison of FIT with other screening tests

For average risk individuals, this thesis focused on the cost-effectiveness of screening with FIT and with gFOBT. The reason is that FOBT was the most likely test to be implemented in a nationwide program in the Netherlands. Other tests which are recommended internationally include flexible sigmoidoscopy and colonoscopy. Now that results on incidence and mortality reduction by sigmoidoscopy have become available in randomized trials,[23,24] the Miscan model (and other models) should be validated against them. The trials showed a very high protective effect of sigmoidoscopy for the distal colon but a small one for the proximal colon. The ongoing colonoscopy trials should shed further light on the effectiveness of endoscopy screening in the distal and proximal colon. The high protective effect in the distal colon indicates a relatively long duration between the occurrence of detectable adenoma and clinical CRC. Depending on how long ago bleeding adenomas started to bleed, this could also be favorable for FIT screening. Endoscopy and FIT should be compared in a cost-effectiveness analysis. Drawbacks of population-wide endoscopy screening in the Netherlands are the low attendance and the invasiveness of especially colonoscopy. Offering individuals a choice between FIT and sigmoidoscopy could become a future screening strategy. The results of such a choice should be determined in population-based studies.

Stopping age for screening

The guidelines of the European Union and some US guidelines advocate to stop screening at age 75. In Chapter 3 we showed that 75 is a reasonable age to stop FIT screening. But from a cost-effectiveness point of view, it would be better to let the stopping age depend on the life expectancy of the individual. Life tables based on co-morbidity can be used for recommending at what age to stop screening in an individual with a certain co-morbidity status.

Surveillance after polypectomy

With the introduction of a nationwide screening program, the number of individuals undergoing polypectomy and subsequently colonoscopic surveillance will steeply increase. The colonoscopy demand will be further enhanced by increased identification of individuals with a CRC family history, who will be advised to switch to colonoscopic surveillance immediately. Risk factors for adenoma recurrence and the implications for the effectiveness of surveillance colonoscopy should be further studied in order to be able to allocate the available colonoscopies to the individuals that would benefit most. It is relevant in this respect that the number and size of the adenomas appeared stronger indicators for the recurrence of adenomas than a family history.[27] This suggests that also for individuals with a family history, the surveillance scheme should primarily be based on adenoma findings at first and later colonoscopies.

Family history risk in relation to family size and age

The family related risk for CRC is usually based on the number of affected relatives and their age at diagnosis. However, individuals with 1 affected relative out of 2 will be at higher risk than those with 1 affected relative out of 10, so family size matters. The ages of the relatives, both the affected and unaffected ones, shold also be taken into account. Finally, someone's family history changes over time. For example, the increased risk due to one affected relative is higher at age 40 of the index person than at age 70. Obviously, risk profiles will be more reliable if they are also based on family size and age of the individual and his or her relatives.

Interaction of family history with other risk factors and implications for personalized screening

Family history is a major risk factor for CRC. Other risk factors include alcohol and red meat consumption, and protective factors like physical activity. These factors will together determine someone's risk profile and therefore the effectiveness and cost-effectiveness of CRC screening. Recently, a risk prediction tool has become available that estimates an indi-

vidual's CRC risk based on a self-administered questionnaire.[28,29] Both family history and lifestyle factor questions are included. With the trend towards personalized medicine, the demand for screening recommendations based on someone's full risk profile will increase.

Use of models

Models develop with the available evidence. With respect to CRC screening, valuable data will become available in the near future from ongoing trials of repeated FIT screening and of colonoscopy screening. Besides, data will increasingly become available from nationwide CRC screening programs. These data can be used to test and improve current assumptions and hypotheses on the natural history of the disease and the test characteristics of different screening tests in simulation models like Miscan-Colon. Models can be very useful to assess the implications of improvements of current tests and the value of new tests for CRC screening. Finally, simulation modeling will be a valuable tool in the light of personalized medicine. With an increasing number of identifiable risk groups, modeling is the only feasible way to evaluate varying screening programs for the different risk groups. But models can never make up for lack of knowledge, and they require thoughtful use.

CONCLUSIONS AND RECOMMENDATIONS

Our results support the following conclusions and recommendations:

- Immunochemical stool testing (FIT) is preferred over guaiac testing, due to the higher attendance, better test characteristics and similar costs.

- In case of sufficient colonoscopy capacity, a low FIT cutoff level for referral to colonoscopy of 50 ng hemoglobin / ml is preferred.

- If colonoscopy capacity is limited, using a high FIT cutoff level is the most important adaptation.

- The increased risk for CRC in individuals with a CRC family history can largely be explained by an increased risk for adenomas.

- FOBT screening programs should be implemented as soon as possible using FIT as the screening test, and countries that currently use gFOBT should change to FIT.

- Colonoscopy capacity should be increased in order to make FIT screening with a low cutoff level possible.

- The frequency of colonoscopy screening for individuals with a family history should be about twice the frequency of those without, depending on the number of first degree relatives with CRC and the age at diagnosis of the affected relatives.

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APPENDIX

Appendix table 1. Assumptions in the MISCAN model for demography and natural history as made in different chapters of this thesis.

	Chapter 3 & 4	Chapter 7	Chapter 8
Demography	Dutch average risk population in 2005[1]	American average risk population from SEER 1993, lifetables from SEER 1989-1991[2]	Birth cohort of American average risk 30-year olds, life tables from SEER 1996-1999[2]
Natural History			
Distribution of risk for adenomas over the general population	Adenoma multiplicity in autopsy studies[3-12]	Adenoma multiplicity in autopsy study[13]	Adenoma multiplicity in autopsy studies[3-12]
Adenoma incidence in general population	Adenoma prevalence in autopsy studies[3-12]	Adenoma prevalence in autopsy and colonoscopy studies[13-17]	Adenoma prevalence in autopsy studies[3-12]
Probability that a new adenoma is progressive	Adenoma prevalence in autopsy studies and Dutch cancer incidence from IKC 1999-2003[3-12,18]	Adenoma prevalence in autopsy and colonoscopy studies and cancer incidence from SEER 1978[2,13-17]	Adenoma prevalence in autopsy studies and SEER cancer incidence 1975-1979[2-12]
Localization distribution of adenomas and cancer	Dutch cancer incidence from IKC 1999-2003 [18]	American cancer incidence from SEER 1978[2]	American cancer incidence from SEER 1975-1979[2]
Stage distribution	Dutch cancer incidence from IKC 1999-2003[18]	American cancer incidence from SEER 1978[2]	American cancer incidence from SEER 1975-1979[2]
Survival after clinical detection	Dutch survival from IKZ 1989-2003, and mortality from IKC 1999-2003[18]	American survival from SEER 1998-2003[2]	American survival from SEER 1996-1999[2]
Survival after screendetected cancer	If the cancer is detected in the same stage as it would have been detected clinically, the survival is assumed the same as a clinically detected cancer in an earlier stage	American survival from SEER 1998-2003[2]	American survival from SEER 1996-1999[2]
Mean duration of development of progressive adenomas to clinical cancer	26.7 years	20 years	20 years
Mean duration of preclinical cancer†	6.7 years	3.6 years	3.6 years
Mean duration of adenoma	20 years	16.4 years	16.4 years
Percent of non-progressive adenomas that stay 6-9mm	50%	50%	50%
Percent of non-progressive adenoma that become 10mm or larger	50%	50%	50%
Percent of cancers that develops from 6-9mm adenoma and from 10+mm adenoma	30% 70%	30% 70%	30% 70%

IKC = Integraal Kanker Centrum SEER = Surveillance, Epidemiology, and End Results

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Summary

Colorectal cancer (CRC) is a major health problem. Worldwide, over 1 million new cases are diagnosed yearly. Twelve thousand of them occur in the Netherlands. CRC is the second cause of cancer death in the Netherlands. About 50% of those diagnosed with CRC die of the disease. Screening can reduce CRC incidence and mortality substantially. Randomized trials have shown a mortality reduction of 11-33% from screening with the guaiac fecal occult blood test (gFOBT), and -recently- 22-31% from sigmoidoscopy screening. In spite of the evidence from the gFOBT trials, the decision to start a population-based screening program has only been made recently in the Netherlands, as in a lot of other European countries.

Immunochemical stool tests (FIT) for CRC screening were introduced more recently than the guaiac tests (gFOBT). The effectiveness of FIT was never investigated in a randomized controlled trial. In chapter 2 we presented results of FIT compared to gFOBT in a randomized trial. The individuals invited were aged between 50 and 75 years. Attendance to FIT was higher than to gFOBT (60 *vs* 50%). The FIT provided quantitative results, allowing a cutoff for referral to colonoscopy to be chosen. In the trial, individuals with a hemoglobin level of 50 ng/mL were referred to colonoscopy. The test characteristics were analyzed for referral levels between 50 and 200 ng/mL. At a cutoff of 75 ng/mL, the number of colonoscopies needed to detect one advanced neoplasia with FIT was comparable to gFOBT, but FIT had a higher yield of advanced neoplasia.

Because of its better attendance, better test characteristics and similar costs, FIT is preferable over gFOBT. The optimal FIT cutoff level for referral to colonoscopy depends on the relative difference in overall costs and effects between screening programmes with different cutoff levels. In chapter 3, we described a cost-effectiveness analysis to make this comparison. We used the micro-simulation model MISCAN-Colon to estimate costs and effects of the screening alternatives. Screening strategies varied by age to start screening (45, 50, 55, 60 years), age to stop screening (70, 75, 80 years) and screening interval (1, 1.5, 2, 3). We found that referring all individuals with a hemoglobin level of 50 ng/mL or more was more cost-effective than at a higher cutoff level. Biennial screening between ages 55-75 years had an incremental cost-effectiveness ratio (ICER) of about 4,000 euro per life-year gained in the base-case analysis. Annual screening within the age range 45-80 years had an ICER of about 15,000 euro per life-year gained.

Next to health effects and cost-effectiveness, the colonoscopy capacity is an issue in CRC screening decisions. This capacity is limited in many countries. Frequent screening or the

use of low cutoff levels for referral to colonoscopy may require too many colonoscopies. Screening programs should therefore be adjusted to meet the available colonoscopy capacity. Possible ways to adapt to a limited colonoscopy capacity are narrowing the screening age range or lengthening the screening interval, using a higher cutoff level for referral to colonoscopy, and restricting colonoscopy surveillance. In chapter 4, we evaluated these alternative strategies in combination with several levels of colonoscopy capacity. In case of an unlimited colonoscopy capacity, the most effective screening strategy with an ICER below 20,000 euro per life-year gained was the annual FIT strategy of screening of individuals aged 45-80 years with referral for a hemoglobin level of 50 ng/ml or more (see also chapter 3). This required 49 colonoscopies per 1000 individuals aged 45-80 per year. In case of a limited colonoscopy capacity, the most important adjustment was an increase in the FIT cutoff level for referral. If the number of colonoscopies per year was limited to 40 per 1000, the optimal cutoff level should be increased from 50 to 75 ng/ml (and the age to start increased slightly from 45 to 50 years). Only if colonoscopy capacity was even lower, fewer screening rounds and less intensive surveillance were good additional ways to further save on colonoscopies. E.g. when the colonoscopy capacity was 20 per 1000 or less, the optimal screening strategy was to refer individuals with a hemoglobin level of 200 ng/ml or more to colonoscopy and to restrict the age range for screening to 50-75 years or smaller. In addition, surveillance was limited by referring individuals with 1 or 2 adenomas smaller than 10 mm back to FIT screening instead of referring them to colonoscopy surveillance. Even for very limited colonoscopy capacity, offering gFOBT instead of FIT was not a preferred way to decrease colonoscopy demand.

In another study, the number of samples per screening round was varied. Offering individuals 2 FIT samples instead of 1 in every screening round, increases the possibility to detect lesions that bleed intermittently. Referring all individuals with at least one positive test out of 2 tests to colonoscopy increases the detection rate compared to screening with 1 sample. At the same time, more individuals are referred to colonoscopy, including more individuals without adenomas or cancer (false positives). In chapter 5, we described the results of a randomized trial of 2 *vs* 1 sample FIT screening, where individuals with at least one test result higher than 50 ng hemoglobin/mL were referred to colonoscopy. Adherence to screening was the same in both arms. At a 50 ng/ml hemoglobin cutoff level for referral to colonoscopy, the proportion of individuals with at least one positive test out of two tests was over 50% higher than the proportion of individuals with a positive test in the 1 sample FIT group (12.8% versus 8.1%). This resulted in a 30% increase of advanced neoplasia detected (4.1% versus 3.1%). So by offering a second test indeed significantly more neoplasia is detected, but the number of colonoscopies needed to

detect is also higher. These are the results for the first screening round only. Implications for a screening program will also depend on the results of subsequent screening rounds.

Individuals with first degree relatives (FDR) affected are at increased CRC risk. These individuals are advised to undergo surveillance with the most sensitive test, namely colonoscopy. The optimal frequency for this surveillance remains to be determined.

The relative risk is 2 for individuals with at least 1 FDR diagnosed with CRC compared to the average risk population. The CRC risk increases with the number of relatives affected and a younger age of diagnosis in these relatives. It is unclear whether the increased risk is caused by having more adenomas or by a faster development of the adenomas. In chapter 6, the results of a comparison of adenoma prevalence in individuals with and without a family history of CRC, and no known genetic disorder, were described. Individuals with a family history appeared to have a higher risk for having adenomas than individuals without (OR=1.75). The number of adenomas is also likely to be higher in these individuals, which increases their risk further. A higher adenoma incidence therefore plausibly explains the increased risk for CRC. A combination with a faster progression of adenomas however remains possible.

The higher risk implicates the need of more frequent screening in individuals with a family history than in those without. In many countries it is currently recommended to screen these individuals with colonoscopy. The recommended colonoscopy frequency differs between countries. In the United States, the recommended screening interval varies between 5 and 10 years, and the recommended age to start screening varies from 40 to 50 years of age. The incremental cost-effectiveness of actively recruiting individuals with a family history in combination with these varying recommendations was determined in chapter 7. Starting at age 40 with a screening interval of 5 years had an ICER of $51,000 per life-year gained compared to 10-year colonoscopy screening starting at age 50, and was to be preferred over the other recommended strategies. In chapter 8, we varied the screening ages over wider ranges. Besides, we looked at individuals with varying familial risk levels for CRC. For individuals with 1 first degree relative diagnosed after age 50, the optimal strategy with a maximum ICER of $50,000 dollar per life-year gained was 6 colonoscopies with a 5 year interval. This compared with 4 colonoscopies every 7 years for average risk individuals. The optimal strategy further increased to 10 colonoscopies every 4 years in case of 1 FDR diagnosed before age 50 years, 13 colonoscopies every 3 years for individuals with 2 or more FDR diagnosed after age 50 years, and 15 colonoscopies every 3 years for individuals with 2 or more FDR of whom at least 1 was diagnosed before age 50 years. Summarizing, the interval for individuals with 1 FDR diagnosed before age 50 or with 2 or more FDRs was approx-

imately half the intervals for average risk individuals (3-4 *vs* 7 years). This is in line with the 50% difference in screening interval as recommended in the guidelines (5 *vs* 10 year intervals).

CONCLUSIONS AND RECOMMENDATIONS:

- Immunochemical stool testing (FIT) is preferred over guaiac testing, due to the higher attendance, better test characteristics and similar costs.

- In case of sufficient colonoscopy capacity, a low FIT cutoff level for referral to colonoscopy of 50 ng hemoglobin/ml is preferred.

- If colonoscopy capacity is limited, using a high FIT cutoff level is the most important adaptation.

- The increased risk for CRC in individuals with a CRC family history can largely be explained by an increased risk for adenomas.

- FOBT screening programs should be implemented as soon as possible using FIT as the screening test, and countries that currently use gFOBT should change to FIT.

- Colonoscopy capacity should be increased in order to make FIT screening with a low cutoff level possible.

- The frequency of colonoscopy screening for individuals with a family history should be about twice the frequency of those without, depending on the number of first degree relatives with CRC and the age at diagnosis of the affected relatives.

SAMENVATTING

Dikkedarmkanker (DDK) is een belangrijk gezondheidsprobleem met meer dan 1 miljoen nieuwe gediagnosticeerde gevallen wereldwijd per jaar en rond de 12.000 in Nederland. Ongeveer 50% van de mensen met DDK sterft aan de ziekte. Daarmee is het de tweede doodsoorzaak aan kanker in Nederland. Screening kan DDK incidentie en sterfte flink reduceren. Gerandomiseerde studies hebben aangetoond dat screening met een guaiac fecaal occult bloed test (gFOBT) de sterfte met 11-33% kan terugdringen. Met een flexibele sigmoidoscopie is de sterftereductie zelfs 22-31%. Ondanks deze gunstige resultaten is de beslissing om een bevolkingsonderzoek voor DDK te beginnen in Nederland,net als in veel andere Europese landen, pas recent genomen.

Fecaal immunochemische ontlastingstesten (FIT) voor DDK screening zijn later geïntroduceerd dan de gFOBT. De effectiviteit van FIT is nog nooit vastgesteld op basis van een gerandomiseerde studie. In hoofdstuk 2 beschrijven we de resultaten van een gerandomiseerde studie waarbij mensen uitgenodigd werden om deel te nemen aan screening met een FIT of gFOBT. De individuen die voor deelname in aanmerking kwamen vielen in de leeftijdscategorie van 50 tot 75 jaar. De deelname aan FIT was hoger dan aan gFOBT (60% vs 50%). De gebruikte FIT geeft een kwantitatieve uitkomst waardoor het mogelijk is een afkapwaarde te kiezen voor doorverwijzing naar diagnostische colonoscopie. In deze studie werden mensen met een hemoglobine gehalte van 50 ng/ml of meer doorverwezen naar colonoscopie. De test karakteristieken zijn ook geanalyseerd voor hogere afkapwaarden (50-200 ng/ml). Bij een afkapwaarde van 75 ng/ml was het aantal benodigde colonoscopieën om met FIT een hoogrisico adenoom te detecteren vergelijkbaar met dat van gFOBT, maar werd met FIT een hoger aantal hoogrisico adenomen gedetecteerd.

FIT is te prefereren boven gFOBT vanwege de hogere deelname, betere test karakteristieken en vergelijkbare kosten. De optimale afkapwaarde van de FIT voor verwijzing naar colonoscopie hangt af van het relatieve verschil in kosten en gezondheidseffecten tussen screeningsprogramma's met verschillende afkapwaarden. In hoofdstuk 3 beschrijven we een kosteneffectiviteitsanalyse op basis waarvan we de optimale afkapwaarde bepaald hebben. Hierbij hebben we gebruik gemaakt van het microsimulatie model MISCAN-Colon om de kosten en effecten van verschillende screeningsalternatieven te schatten. Screeningsstrategieën varieerden met betrekking tot de startleeftijd (45, 50, 55, 60 jaar), de stopleeftijd (70, 75,80 jaar) en het screeningsinterval (1, 1,5, 2, 3 jaar). Het bleek kosteneffectiever om alle individuen met een hemoglobine gehalte

van 50 ng/ml of meer door te verwijzen naar colonoscopie dan om een hogere afkapwaarde te gebruiken. De incrementele kosteneffectiviteitsratio (IKER) van tweejaarlijks screenen van individuen in de leeftijd 55-75 jaar was ongeveer 4.000 euro per gewonnen levensjaar. Jaarlijks screenen in de leeftijd 45-80 jaar had een IKER van ongeveer 15.000 euro per gewonnen levensjaar.

Naast gezondheidseffecten en kosteneffectiviteit is ook colonoscopiecapaciteit van invloed op beslissingen rondom DDK screening. De capaciteit is namelijk beperkt in veel landen. Frequente screening of het gebruik van lage afkapwaarden voor verwijzing naar colonoscopie kunnen tot te veel colonoscopieën leiden. In dat geval moeten screeningsprogramma's dusdanig aangepast worden dat het aantal benodigde colonoscopieën ook beschikbaar is. Mogelijke manieren om een screeningsprogramma aan een beperkte colonoscopiecapaciteit aan te passen zijn een oudere startleeftijd en/of een jongere eindleeftijd, een langer screeningsinterval, het gebruik van een hogere afkapwaarde voor verwijzing naar colonoscopie en het beperken van het aantal surveillance colonoscopieën. In hoofdstuk 4 hebben we deze alternatieven met elkaar vergeleken voor verschillende capaciteitsniveaus. In geval van een onbeperkte colonoscopiecapaciteit was de meest effectieve screeningsstrategie met een IKER lager dan 20.000 euro per gewonnen levensjaar de hierboven genoemde FIT strategie met jaarlijkse screening tussen leeftijden 45-80 en een afkapwaarde van 50 ng hemoglobine/ml (zie ook hoofdstuk 3). Dit vereiste 49 colonoscopieën per 1000 individuen in de leeftijd 45-80 jaar. Als de colonoscopiecapaciteit beperkt is, is de belangrijkste aanpassing het gebruik van een hogere afkapwaarde voor de FIT. Als het aantal colonoscopieën beperkt was tot 40 per 1000, dan nam de afkapwaarde toe van 50 tot 75 ng-ml (en de startleeftijd nam iets toe van 45 tot 50 jaar). Alleen als de colonoscopiecapaciteit nog lager was, werden minder screeningsrondes en minder intensieve surveillance goede additionele aanpassingen om het benodigde aantal colonoscopieën verder te reduceren. Als de colonoscopiecapaciteit bijvoorbeeld 20 per jaar of minder was, dan was de optimale screeningsstrategie het doorverwijzen van individuen met een hemoglobine gehalte van 200 ng/ml of meer en beperking van het leeftijdsinterval tot 50-75 of smaller. Bovendien was het aantal surveillance colonoscopieën verminderd door individuen met 1 of 2 adenomen kleiner dan 10 mm naar FIT terug te verwijzen in plaats van naar surveillance colonoscopie. Zelfs bij een zeer beperkte colonoscopie capaciteit was het gebruik van gFOBT in plaats van FIT geen goede manier om de colonoscopiecapaciteit te reduceren.

Een andere manier om FIT screening te optimaliseren is door het aantal testen per screeningsronde te variëren. Door individuen 2 in plaats van 1 test aan te bieden neemt

de kans toe dat een lesie die af en toe bloed wordt gevonden. Als iedereen met tenminste 1 positieve test van de 2 testen wordt doorverwezen naar colonoscopie, neemt het aantal gedetecteerde adenomen en kankers toe vergeleken met 1 test. Tegelijkertijd worden meer mensen doorverwezen naar colonoscopie, waaronder meer mensen zonder adenomen of kanker (fout-positieven). In hoofdstuk 5 beschrijven we de resultaten van een gerandomiseerde studie waarbij 2 testen per screeningsronde vergeleken zijn met 1 test. In deze studie werden individuen met tenminste 1 testuitslag hoger dan 50 ng hemoglobine/ml doorverwezen naar colonoscopie. De opkomst was in beide groepen gelijk. Bij een afkapwaarde van 50 ng/mL hemoglobine voor verwijzing naar colonoscopie is de proportie individuen met tenminste 1 positieve test van de 2 testen meer dan 50% hoger dan de proportie individuen met een positieve test in de 1 sample groep (12.8% versus 8.1%). Dit resulteerde in een 30% toename van het aantal gedetecteerde hoogrisico adenomen (4.1% versus 3.1%). Er worden dus inderdaad meer hoogrisico adenomen gedetecteerd bij het gebruik van een tweede test, maar het aantal benodigde colonoscopieën is ook hoger. De beschreven resultaten zijn alleen van de eerste screeningsronde. Implicaties voor een screeningsprogramma hangen ook af van de resultaten van vervolgrondes.

Individuen met een familiegeschiedenis van DDK hebben een verhoogd risico op de ziekte. Deze individuen wordt geadviseerd surveillance te ondergaan met de meest sensitieve test, de colonoscopie. De optimale surveillance frequentie moet nog worden vastgesteld. Het relatieve risico is 2 voor mensen met tenminste 1 eerstegraads familielid met DDK vergeleken met de gemiddelde risico populatie. Het risico op DDK neemt toe met het aantal familieleden met de ziekte en een jongere leeftijd waarop de ziekte bij deze familieleden is gediagnosticeerd. Het is onduidelijk of het verhoogde risico veroorzaakt wordt door een verhoogd aantal adenomen of door een versnelde groei van de adenomen. In hoofdstuk 6 wordt de adenoomprevalentie in individuen met en zonder een DDK familiegeschiedenis (van wie geen genetische afwijking bekend is) vergeleken. Individuen met een familiegeschiedenis bleken een hoger risico te hebben op de aanwezigheid van adenomen (OR=1.75). Het is bovendien zeer waarschijnlijk dat het aantal adenomen in deze individuen ook hoger is waardoor het risico op DDK nog verder toe zou nemen. Het is daarom aannemelijk dat het verhoogde risico op DDK in deze individuen wordt veroorzaakt door een verhoogde adenoom incidentie. Een combinatie met een snellere groei blijft echter mogelijk.

Het hogere risico impliceert vaker screenen van individuen met een familiehistorie dan van individuen zonder. In veel landen wordt momenteel aanbevolen om deze indivi-

duen met colonoscopie te screenen. De aanbevolen screeningsfrequentie wisselt tussen landen. In de Verenigde Staten varieert het aanbevolen interval tussen de 5 en 10 jaar. De aanbevolen startleeftijd varieert van 40 tot 50 jaar. De incrementele kosteneffectiviteit van het rekruteren van individuen met een familiegeschiedenis in combinatie met deze variërende aanbevelingen wordt beschreven in hoofdstuk 7. Screenen vanaf leeftijd 40 met een interval van 5 jaar resulteerde in een IKER van $51.000 per gewonnen levensjaar ten opzichte van screenen met een 10-jaars interval en een startleeftijd van 50 jaar en is te prefereren boven de andere strategieën. In hoofdstuk 8 zijn de screeningsleeftijden gevarieerd over bredere intervallen. Bovendien hebben we naar individuen met een verschillend risiconiveau gekeken. Voor individuen met een eerstegraads familielid gediagnosticeerd na leeftijd 50 was de optimale strategie, bij een maximum IKER van $50.000 per gewonnen levensjaar, 6 colonoscopieën met een 5-jaars interval. Dit is te vergelijken met 4 colonoscopieën elke 7 jaar voor de gemiddelde risico populatie. Het optimale aantal colonoscopieën nam verder toe tot 10 colonoscopieën elke 4 jaar in geval van 1 eerstegraads familielid gediagnosticeerd voor leeftijd 50, 13 colocoscopien elke 3 jaar voor individuen met 2 of meer eerstegraads familieleden gediagnosticeerd na leeftijd 50, en 15 colonoscopieën elke 3 jaar voor individuen met 2 of meer eerstegraads familieleden van wie er tenminste 1 gediagnosticeerd is voor leeftijd 50. Samengevat, het interval voor individuen met 1 eerstegraads familielid gediagnosticeerd voor leeftijd 50 of met 2 of meer eerstegraads familieleden was ongeveer de helft van het interval voor gemiddelde risico individuen (3-4 versus 7 jaar). Dit komt overeen met het 50% verschil in screeningsinterval zoals aanbevolen in de richtlijnen (5 versus 10 jaars intervallen).

Conclusies and aanbevelingen

- Immunochemische ontlastingstesten zijn te prefereren boven guaiac ontlastingstesten vanwege de hogere opkomst, betere testkarakteristieken en vergelijkbare kosten.

- Bij voldoende colonoscopiecapaciteit is een lage afkapwaarde van de FIT voor doorverwijzing naar colonoscopie van 50 ng hemoglobine / ml te prefereren.

- Als de colonoscopiecapaciteit beperkt is, is het gebruik van een hoge afkapwaarde van de FIT de belangrijkste aanpassing.

- Het verhoogde risico op DDK bij individuen met DDK familiegeschiedenis kan voor een groot deel worden verklaard uit een verhoogd risico op adenomen.

- Screeningsprogramma's met een FOBT zouden zo snel mogelijk moeten worden ingevoerd met FIT als screeningstest, en landen die momenteel een gFOBT gebruiken zouden moeten overstappen op een FIT.

- Colonoscopiecapaciteit zou uitgebreid moeten worden om FIT screening met lage afkapwaarden mogelijk te maken.

- Individuen met een DDK familiegeschiedenis zouden twee maal zo vaak gescreend moeten worden als individuen zonder, afhankelijk van het aantal eerstegraads familieleden en de leeftijd waarop DDK gediagnosticeerd werd.

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Curriculum Vitae

Janneke Wilschut werd geboren op 10 januari 1977 te Leiderdorp. In 1995 behaalde zij het VWO diploma aan het Vlietland College te Leiden. In datzelfde jaar begon zij aan de studie econometrie aan de Vrije Universiteit te Amsterdam. In 2000 heeft zij aanvullend een semester aan de Universidad Computense te Madrid gevolgd. In 2001 heeft zij een half jaar stage gelopen bij OPG Groothandel waar ze onderzoek deed naar optimale voorraadstrategieën. Dit was tevens het onderwerp van haar afstudeerscriptie, waarmee ze in 2002 haar studie Econometrie afrondde in de richting operationele research. In 2003 startte ze bij TNO Defensie en Veiligheid, waar ze onderzoek deed naar operationele aspecten van militair optreden. Vanaf 2005 werkte ze aan de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC te Rotterdam. Ze heeft hier onderzoek gedaan naar de kosten en effecten van dikkedarmkanker screening met behulp van het microsimulatie model MISCAN-Colon. Sinds 2011 werkt ze aan de afdeling Innovaties & Publieke Sector Efficiëntie Studies van de Technische Universiteit Delft.

PhD Portfolio

Name PhD student: Drs. Janneke Wilschut
Erasmus MC Department of Public Health

PhD period: 2005-2012
Promotor: Prof. dr. J.D.F. Habbema
Prof. Dr. E. J. Kuipers
Supervisor: dr. M. Van Ballegooijen

PhD training	Year	Workload (Hours)
Courses		
Nihes, Erasmus MC, Rotterdam		
- Planning and evaluation of screening	2006	40
- Case-control studies	2006	20
- Cohort Studies	2006	20
- Topics in meta-analysis	2007	20
Presentations		
Presentations at Public Health Department, Erasmus MC, Rotterdam	2005-2010	40
Presentations at Cancer Intervention and Surveillance Modelling Network (CISNET), National Cancer Institute, Bethesda	2005-2007	40
Digestive Disease Week		
- Optimal screening policies for individuals with a family history of colorectal cancer (poster)	2009	20
American Society of Clinical Oncology Meeting, Orlando	2010	20
- Cost-effectiveness analysis comparing a guaiac fecal occult blood test with a quantitative immunochemical test at different cutoff levels (poster)		
Digestive Disease Week, New Orleans		
- Should we offer individuals two samples of an immunochemical fecal occult blood test for colorectal cancer screening instead of one? A cost-effectiveness analysis (poster)	2010	20
- Quantitative immunochemical fecal occult blood screening under a colonoscopy constraint: a higher cutoff level, a smaller age range or a longer screening interval? A cost-effectiveness analysis (poster of distinction)	2010	20

International Cancer Screening Network, Oxford - Cost-effectiveness analysis comparing a guaiac fecal occult blood test with a quantative immunochemical test at different cutoff levels	2010	40

International conferences

European School of Oncology – Colorectal Cancer Conference, Londen	2005	16
American Society of Clinical Oncology Meeting, Orlando	2010	40
Digestive Disease Week, New Orleans	2010	40

Seminars and workshops

Seminars at the department of Public Health, Rotterdam	2005-2010	100
Evidentie en beslissen in de Gezondheidszorg: Stand van wetenschap en praktijk, Rotterdam	2010	4
International Cancer Screening Network Meeting, Oxford	2010	24

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