Effects of colorectal cancer screening on population health
- a modeling assessment -

Iris Lansdorp-Vogelaar

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- a modeling assessment -

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- een model evaluatie -

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Voor papa

zonder wie ik
nooit aan dit
avontuur
begonnen
zou zijn

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Publications

The chapters in this thesis are based on the following publications:

Chapter 2:
Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, Zauber AG, Habbema JDF. A novel hypothesis on the sensitivity of FOBT - Results of a joint analysis of three randomized controlled trials. Cancer *in press*.*

Chapter 3:
Vogelaar I, van Ballegooijen M, Schrag D, Boer R, Winawer SJ, Habbema JDF, Zauber AG. How much can current interventions reduce colorectal cancer mortality in the U.S.? Mortality projections for scenarios of risk factor modification, screening, and treatment. Cancer 2006;107:1624-33.*

Chapter 4:
Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut JA, Habbema JDF. At what costs will screening with CT colonography be competitive? A cost-effectiveness approach. Int J Cancer 2009;124:1161-8.*

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Chapter 6:
Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut JA, Winawer SJ, Habbema JDF. Individualizing colonoscopy screening by sex and race. Gastrointest Endosc *in press*.*

Chapter 7:
Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut JA, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149:659-69.*

Chapter 1: Introduction

1.1 Colorectal cancer epidemiology

Colorectal cancer (CRC) is the second leading cause of cancer death in the Netherlands and other developed countries.[1] Each year, more than 10,000 cases are newly diagnosed in the Netherlands[2] and over 1 million worldwide.[3] About half of these patients die of the disease. CRC is most common in Europe, North America, Australia and Japan (Figure 1.1). The Western diet is the most likely cause for the high incidence in these countries.[4, 5] This causation is supported by the increasing trend in CRC incidence in newly industrialized countries[6, 7] and the high CRC incidence in non-Western immigrants in for example the U.S. and Australia.[8, 9]

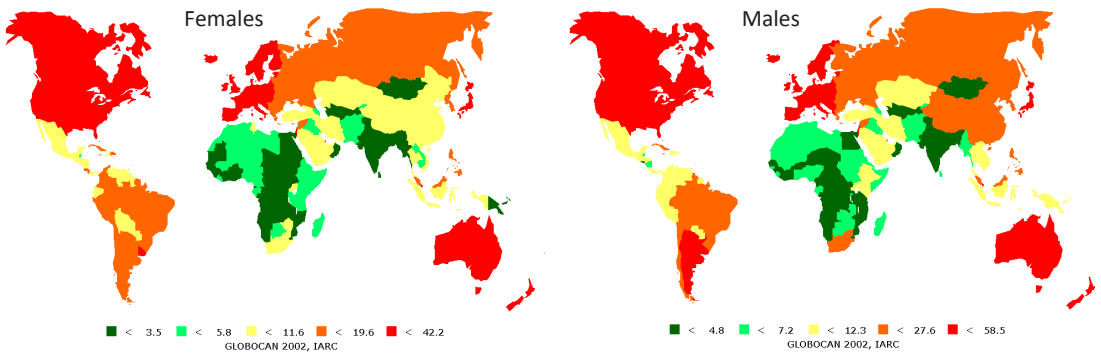

Figure 1.1: Age-standardized CRC incidence by country (rate per 100,000)[3]

Figure 1.2 shows CRC mortality by age for men and women in the Netherlands.[2] CRC is mainly a disease of the elderly population. Incidence and mortality before age 50 are rare and mostly caused by hereditary disorders like familial adenomatous polyposis (FAP) and hereditary non-polyposis CRC (HNPCC). Men have a higher age-specific CRC risk than women. However because women tend to live longer than men, the absolute number of CRC cases is similar for men and women (in the Netherlands: 5,157 and 4,741 cases respectively).

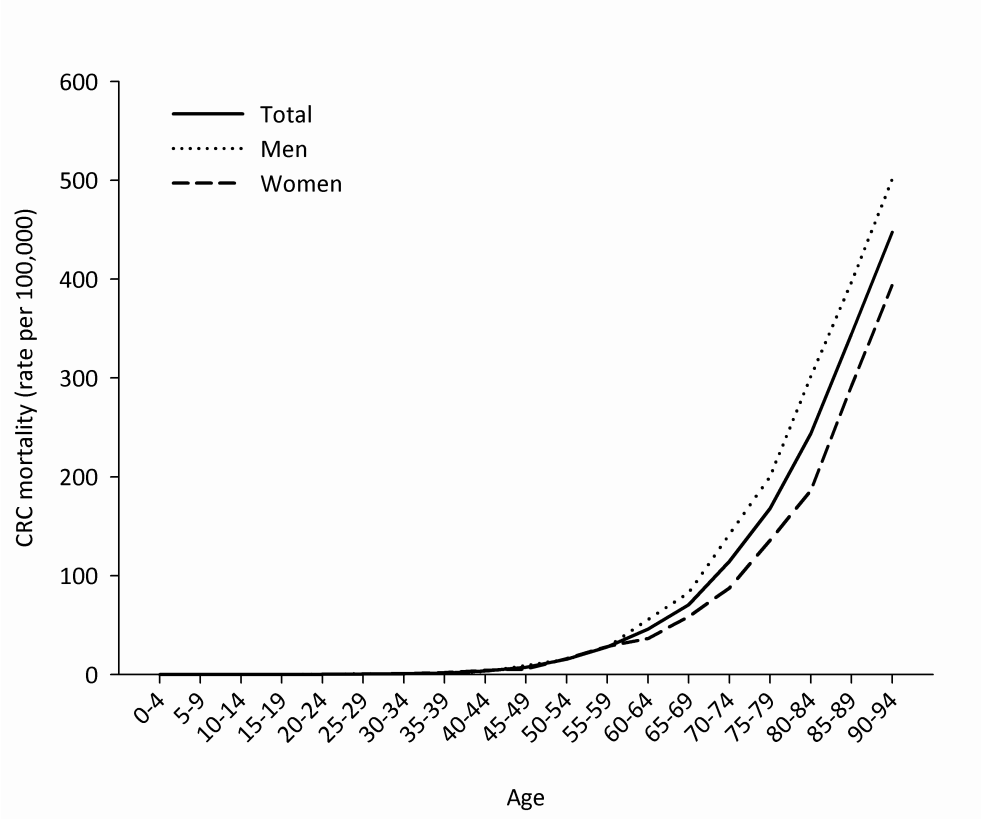

Figure 1.2: Age-specific CRC mortality by gender in the Netherlands (rate per 100,000)[2]

Besides diet, other risk factors for CRC are obesity (Relative Risk (RR) obese compared to not obese = 1.5)[10, 11] and smoking (RR = 1.8)[12, 13]. Protective factors are physical activity (RR = 0.6)[10, 11], multivitamin use (RR = 0.7)[14-16] and aspirin intake (RR = 0.5)[17-19].

1.2 Colorectal cancer as a public health problem

CRC is an important health problem. In the Netherlands for example, 4,451 people died of CRC in 2003, resulting in 56,382 life-years lost relative to the life expectancy without CRC.[20] At the same time, there were 39,898 patients alive with a diagnosis of CRC within the past 10 years.[20] Together, these patients required € 232.4 million for CRC treatment (Figure 1.3).[21] By 2005, these costs had increased to € 273.2 million.[21] This increase was due to ageing of the population and increasing costs for CRC management.

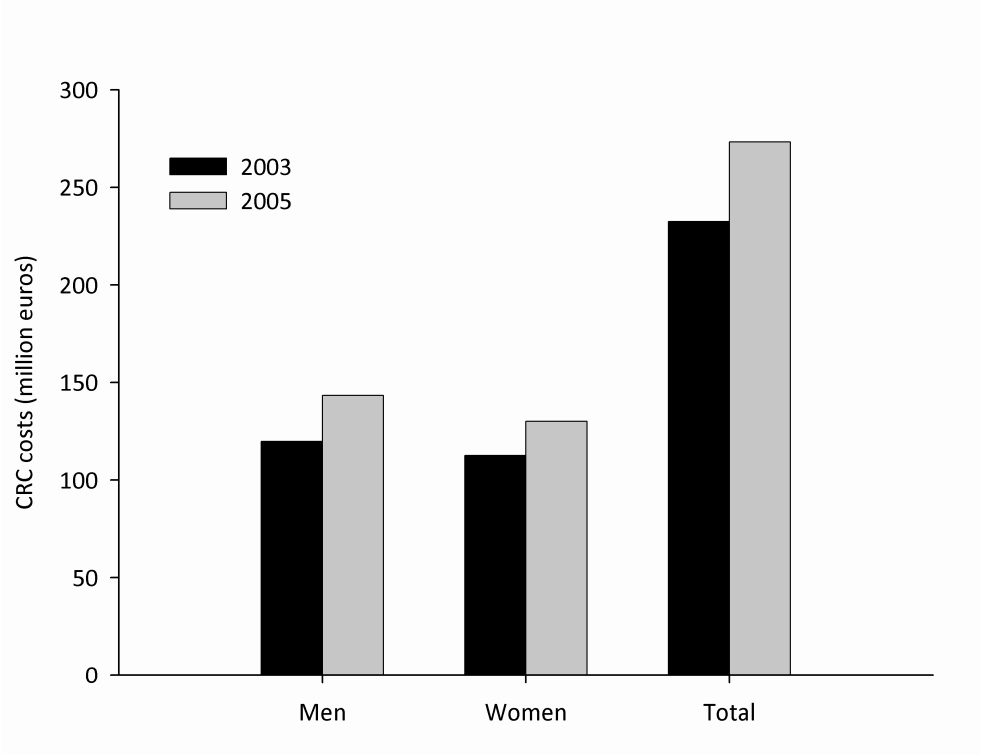

Figure 1.3: Costs for the management of CRC in the Netherlands, by gender and calendar year [21]

1.3 The colorectum

The colorectum is approximately 1.5m long and is generally subdivided into 6 different parts (Figure 1.4). Rectum to descending colon is called the distal or left part, transverse colon to cecum proximal or right part. The cecum starts where the small bowel ends and the rectum opens to the outside at the anus.

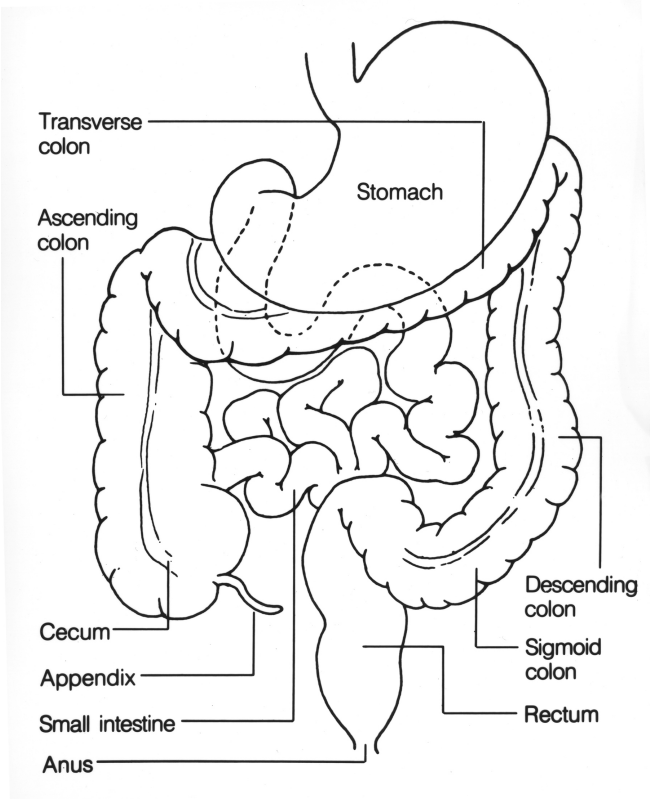

Figure 1.4: Schematic overview of the colorectum (Source: U.S. National Cancer Institute)

1.4 Natural history

CRC is generally assumed to develop from adenomas, according to the adenoma-carcinoma sequence (Figure 1.5).[22, 23] Adenomas can occur anywhere in the colorectum after a series of mutations that cause dysplasia of the epithelium. Larger adenomas are most often pedunculated, but can also be sessile or flat.[24] An adenoma grows in size and can develop high-grade dysplasia. At a certain point in time, the adenoma can invade the mucosa and become malignant. In general, this malignant cancer initially does not give symptoms (preclinical cancer). Somewhere in the process from localized (stage I) to metastasized (stage IV) cancer, the cancer causes symptoms and will be diagnosed (clinical cancer). As a result, some cancers are diagnosed in an early, localized stage, others only when disseminated. In developed countries such as the U.S., approximately 40-50% of the population develop one or more adenomas in a lifetime[24] but the large majority of these adenomas will never develop into CRC. Only 5-6% of the population actually develop CRC in their lifetime.[25] The average duration of the adenoma-carcinoma sequence is unobservable, but it is estimated to take at least 10 years.[26]

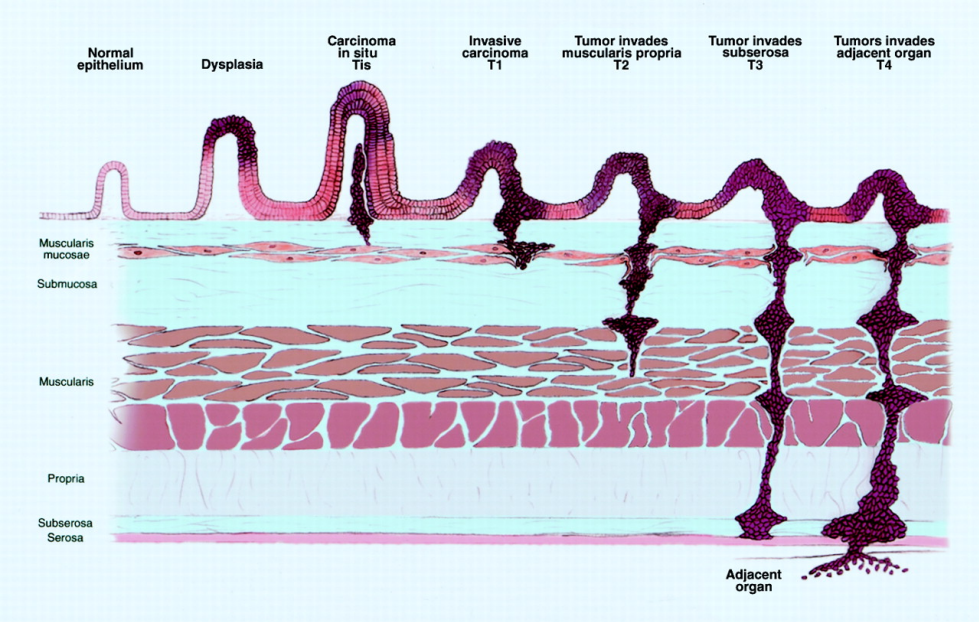

Figure 1.5: Diagram of adenoma—carcinoma sequence shows development of colon cancer and corresponding primary tumor (T) stage (Source: Iyer et al. AJR 179(1), Reprinted with kind permission from the American Journal of Roentgenology)

Without screening, approximately 50% of CRC cases is detected in an advanced stage (stage III or IV, Figure 1.6).[2] Despite improvement in diagnostics and education of the population, this percent has remained stable over the past years. Stage of diagnosis is an important determinant of prognosis. Figure 1.7 shows that 5-years relative survival for stage I disease is 90%, whereas 5-years survival for stage IV disease is about 5%.[2]

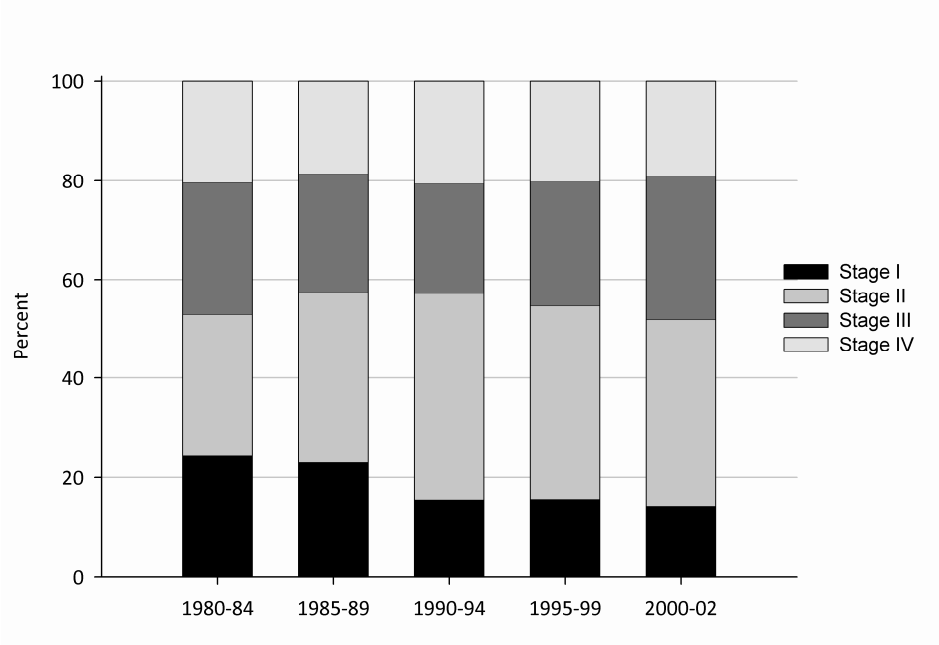

Figure 1.6: Trends in stage distribution of colorectal cancer in the south of the Netherlands[2]

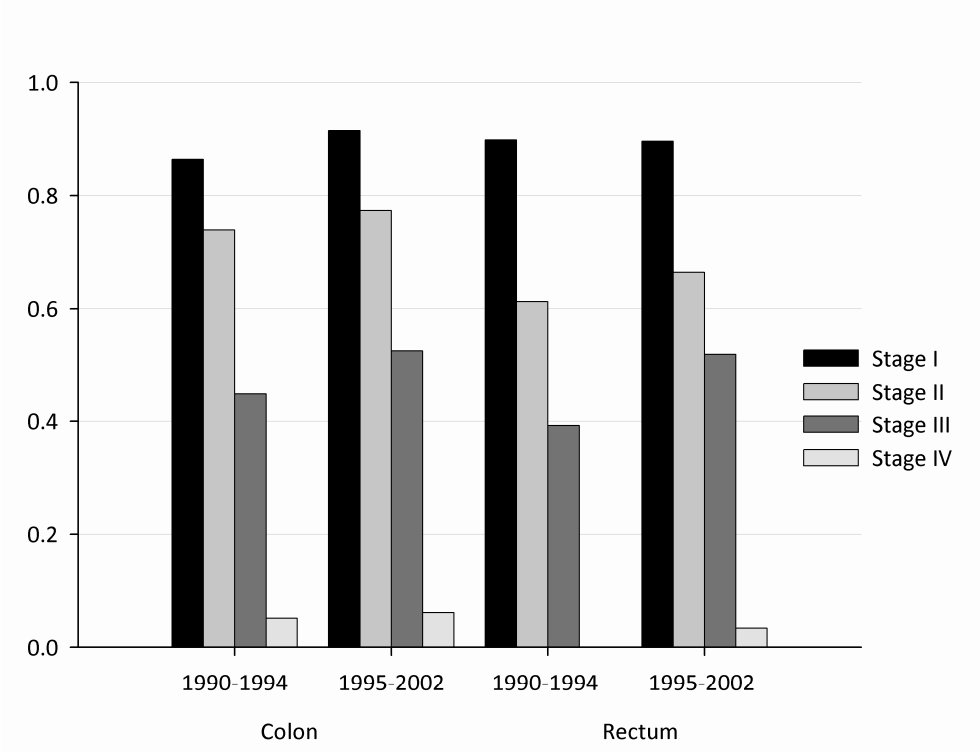

Figure 1.7: Trends in 5-years relative survival of colon and rectal cancer patients in the south of the Netherlands[2]

1.5 Colorectal cancer prevention

Primary prevention

There are several types of interventions for preventing CRC deaths. Methods for primary prevention include adopting a healthy lifestyle and applying chemoprevention (e.g. aspirin or cox inhibitors). Established risk factors for CRC are smoking, eating red meat and being obese, whereas physical activity, multivitamin use and aspirin use have a protective effect. A cohort study among middle-aged men in the U.S. has shown that seventy percent of colon cancers potentially would be preventable by modifying risk factor behavior. However, changing lifestyle has proven to be hard to accomplish and currently available chemoprevention drugs were shown to have an excess risk for bleeding or cardiovascular disease.[27]

Secondary prevention / screening

CRC is especially suitable for screening. Effective screening requires a long screendetectable latent phase and improved prognosis when treatment is done during this phase. As noted above, the adenoma-carcinoma sequence is estimated to take at least 10 years on average. If detected at the adenoma stage, removal of the adenoma prevents incidence of CRC. The fact that 5-years survival for stage I disease is more than 90%, whereas 5-years survival for stage IV disease is less than 5% (Figure 1.7), shows that early detection of cancer can also prevent CRC death.

A whole range of tests is available for CRC screening (Table 1.1). The tests can be divided into three categories: stool tests, endoscopy tests and imaging tests. There are three types of stool tests: the guaiac fecal occult blood test (FOBT), the immunochemical FOBT, also known as fecal immunochemical test (FIT) and the stool DNA test. With FOBT, stool samples are tested for the presence of occult blood. The guaiac FOBT tests for the presence of any blood, whereas the immunochemical FOBT is specific for human blood. The stool DNA test detects DNA mutation markers in stool shed by neoplastic lesions.

Table 1.1: Available CRC screening tests and level of evidence of their effectiveness

CRC screening test	Available evidence for effectiveness
Stool tests	
Guaiac FOBT (Hemoccult II)	11-33% CRC mortality reduction from four RCTs[28-31]
Immunochemical FOBT	32% rectal cancer mortality reduction from one RCT[32] 50-80% CRC mortality reduction from case-control studies[33, 34] Back-to-back studies in screening population showed superior sensitivity compared to guaiac FOBT[35-40]
Stool DNA	No studies on mortality reduction Back-to-back studies in symptomatic patients showed better sensitivity but worse specificity than guaiac FOBT[41, 42]
Endoscopy	
Flexible sigmoidoscopy	80% CRC incidence reduction from RCT (50% mortality reduction, but non-significant)[43] 59-79% CRC mortality reduction from case-control studies[44-46]
Colonoscopy	76-93% CRC incidence reduction from cohort study,[47] 39-53% from case-control study[48] 57% CRC mortality reduction from case-control study[44]
Imaging techniques	
Barium enema	No studies on mortality reduction Back-to-back studies in symptomatic patients showed inferior sensitivity and specificity compared to colonoscopy[49]
CT Colonography	No studies on mortality reduction Back-to-back studies in screening population showed similar sensitivity for large adenomas and cancer compared to colonoscopy[50, 51]

RCT = randomized controlled trial.

The guaiac FOBT Hemoccult II is the only test for which evidence of its effectiveness has been tested by multiple randomized controlled trials (RCTs). Four trials have consistently shown that this FOBT can reduce CRC mortality by 11-33% (Table 1.2).[28-31] One Japanese RCT showed a 32% rectal cancer mortality reduction from a once-only immunochemical FOBT.[32] Furthermore, there have been at least two case-control studies suggesting that screening with immunochemical FOBT reduces CRC mortality.[33, 34] Finally, comparative studies of guaiac and immunochemical FOBT have shown that immunochemical FOBT is more sensitive than guaiac FOBT.[35-40] For some cut-off levels for referral, immunochemical FOBT was also more specific.[37, 38] The stool DNA test is a relatively new test that is

still under development. There is no evidence on mortality reduction from stool DNA testing. In general, stool DNA screening is found to be at least equally sensitive as Hemoccult II screening, but with considerably lower specificity.[41, 42] Studies showing more promising test characteristics tend to have small symptomatic sample populations, and results need to be confirmed by larger studies in the asymptomatic average-risk population.

Table 1.2: Overview of randomized controlled trials on the effectiveness of guaiac FOBT screening with Hemoccult II

Study	Age range	Interval	CRC mortality reduction	# FU years	# Screen rounds
Nottingham*	45-75	2-year	13% (CI 0.78-0.97)	11 years	3-6
Funen†	45-74	2-year	11% (CI 0.78-1.01)	17 years	9
Minnesota	50-80	2-year	21% (CI 0.62-0.97)	18 years	6
Minnesota	50-80	1-year	33% (CI 0.51-0.83)	18 years	11
Goteborg	60-64	2-year	16% (CI 0.78-0.90)	15.5 years	2-3

CRC = colorectal cancer; FU = follow-up.

* Non-attenders were initially not re-invited.

† Non-attenders were not re-invited.

With endoscopy screening a flexible tube with a fiber optic camera is inserted into the colorectum. With this procedure, the physician can detect abnormalities and remove or biopsy them in the same procedure. The two main endoscopy procedures are (flexible) sigmoidoscopy and colonoscopy. Both procedures are highly sensitive for adenomas as well as cancer.[52, 53] With sigmoidoscopy less than half of the colorectum is inspected. Currently, four randomized controlled trials are being conducted on the CRC mortality reduction by sigmoidoscopy screening.[54-57] A small randomized controlled trial in Telemark has shown that sigmoidoscopy screening reduces CRC incidence by 80%, but the study was underpowered to show a significant reduction in CRC mortality.[43] Case-control studies have suggested that sigmoidoscopy screening can reduce CRC mortality by 59-79%.[44-46] Colonoscopy generally reaches the whole colorectum. There have not been any randomized controlled trials on the effectiveness of colonoscopy, although there are plans for a multicenter trial in Norway, Poland, Iceland and the Netherlands. Data from the National Polyp Study suggest that CRC incidence can be reduced by 76-93% in adenoma patients by colonoscopy with polypectomy and subsequent periodic control colonoscopies (surveillance).[47] The major drawback of colonoscopy screening is that it is an expensive and invasive testing method and not without risk.[58, 59]

There are two imaging techniques available for CRC screening: barium enema and Computed Tomographic Colonography (CTC). Barium enema is an X-ray examination of the colorectum. There is no evidence on the effectiveness of barium enema in reducing CRC mortality. Sensitivity is estimated to be high for larger polyps and CRC, but these estimates are mainly based on studies in high-risk individuals.[49] The use of barium enema is declining because of its labor-intensive nature, the low reimbursement rate, and greater interest in newer and more sophisticated technologies such as CTC. With CTC, two CT scans are made of the colorectum. From these scans, two- and three-dimensional images are constructed to investigate the presence of lesions in the colon and rectum. Like for

barium enema, no evidence on mortality reduction is available. Comparative studies in screening populations have shown that sensitivity of CTC for cancer and large polyps may be comparable to that of colonoscopy.[50, 51] A limitation of both imaging techniques is that colonoscopy is required to further confirm and remove abnormalities detected.

Treatment

In recent years, treatment of CRC has improved significantly, especially for rectal cancer. The acceptance of the principle of total mesorectal excision for rectal cancers has ensured significant improvements in the quality of surgical resection.[60] Pre-surgical radiotherapy for these tumors has allowed the possibility of down-staging making more rectal cancers suitable for total mesorectal excision, with a reduced local recurrence rate during long-term follow-up.[61] Also, recent advances in treatment of metastatic disease such as portal vein embolization, have made liver resection a possibility for more patients. The criteria for resectability are also less rigid than in the past and the tendency to adopt a more aggressive treatment of metastatic lesions is the rule.[62, 63] This approach is associated with prolonged survival for patients with liver metastases.[64]

In terms of systemic management, 5-fluorouracil (5-FU) with leucovorin, has been the mainstay of chemotherapy for CRC in both the adjuvant and metastatic settings for a long time. In the late 1990s, the introduction of irinotecan and oxaliplatin as combination treatment with 5-FU/leucovorin increased the median survival of patients with disseminated CRC from 14 to 16 months. Sequential chemotherapy of both irinotecan and oxaliplatin with 5-FU/leucovorin further increased this survival to 21 months. Yet more recently, several biopharmaceuticals, in particular the monoclonal antibodies bevacizumab and cetuximab, have shown promise in clinical studies[65, 66] and are rapidly being implemented in regular treatment protocols.

1.6 Status of colorectal cancer screening

Although the improvements in survival from the new chemotherapies are substantial and primary prevention bears potential in the long run, screening so far seems to offer the best possibility for reducing CRC mortality. CRC screening is also the focus of this thesis. Despite the evidence for the effectiveness of guaiac FOBT screening, CRC screening has not been implemented in the Netherlands yet. In a consensus-meeting in 2005, all Dutch stakeholders in the field of CRC screening (i.e. clinicians, epidemiologists, decision analysts, screening organizations, policy makers, patient coalitions, health council etc.) agreed that a national FOBT screening program should be implemented.[67] Before implementation, pilot studies needed to be carried out to determine population acceptability and detection rates of different FOB tests. These studies show that immunochemical FOBT screening is most acceptable to the Dutch population and is superior to guaiac FOBT with respect to detection rates.[68] It is planned that the Dutch government will make a decision on the implementation of a national CRC screening program in 2010. Creating sufficient endoscopy capacity will be the biggest challenge for the outroll of a national screening program.

The European Union recommends guaiac FOBT screening of all people in the ages 50 to 74.[69] They currently do not recommend any of the other tests, because the extent of effectiveness of these

more expensive tests has not (yet) been established by randomized controlled trials. Several European countries are currently in the process of implementing a national population screening program.[70] In five countries, population-based programs are currently being rolled out nationwide (Finland, France, Italy, Poland and the United Kingdom). Furthermore, seven countries have established nationwide non-population-based programs (Austria, Bulgaria, Czech Republic, Germany, Greece, Latvia and Slovak Republic). Another five countries are currently planning or piloting a nation-wide population-based program (Hungary, Cyprus, Portugal, Romania and Slovenia). Out of these seventeen countries, ten have adopted only FOBT, six use both FOBT and endoscopy and one only colonoscopy.

In the U.S., all screening strategies mentioned in Table 1.1 are considered acceptable screening methods for the general population.[71] The FOBT and endoscopy tests are currently reimbursed by Medicare and other health care insurers.

1.7 Colorectal cancer modeling

The different screening programs throughout Europe and the rest of the world reflect uncertainty about which strategy is best and differences in decision-making processes regarding e.g. which evidence is sufficient. Microsimulation models can help inform policy makers. Once randomized controlled trials have determined the efficacy of a screening test, models can extrapolate the trial results to different screening ages and intervals. Moreover, models can be used to determine comparative (cost-)effectiveness of different tests and estimate the burden of a CRC screening program on available capacity and resources.

Several CRC screening models have assessed the cost-effectiveness of CRC screening. All agreed that CRC screening is cost-effective compared to no screening, but they disagreed on which strategy was most cost-effective.[72] The Institute Of Medicine (IOM) recognized this problem and invited the modelers to participate in a workshop in January 2004 to explore model differences and see if differences could be reduced when standardizing key inputs.[73] Five modelers agreed to participate. Each model estimated costs and life-years gained for five different screening strategies. Each estimation was done twice: once with the original model assumptions as being used by the modelers and once with standardized input assumption as specified by the workshop organizers. Standardized model inputs concerned test and treatment costs, test performance, compliance to screening and the surveillance protocol. As expected, there was quite some variation in the optimal screening strategies with the original modelers' assumptions. After standardization of model assumptions, there was still considerable variation in absolute levels of costs and life-years gained, but interestingly the ordering of strategies with respect to cost-effectiveness were very comparable. Based on these results, the workshop organizers concluded that variation in results between CRC models could be reduced when standardizing inputs for costs, test performance, compliance and surveillance.

1.8 CISNET

Although the results of the IOM modeling workshop were promising, some differences remained between the models that could not be explained by the parameters explored. In an attempt to provide an opportunity for modelers to cooperate with each other and identify reasons for discrepancies in model results, the National Cancer Institute (NCI) in the U.S. had established the Cancer Intervention and Surveillance Modeling Network (CISNET) in September 2000.[74] In this project, different models work cooperatively to estimate the impact of cancer control interventions on cancer trends. While each modeler has areas of individual focus, whenever possible, a common "base" question is developed that allows for comparison across models. In these common "base" case collaborations, a set of common population inputs is used across all models (e.g., dissemination patterns of screening and treatment, mortality from non-cancer causes), and a common set of intermediate and final outputs is developed to help understand differences and similarities across models.

The idea behind this cooperation is that by working together models are improved and modeling work becomes more transparent. Furthermore, modelers establish which is best available data to inform the models and this way reduce variation in model outcomes. There are currently four different cancer sites considered in CISNET: lung, breast, prostate and colorectal. For each site, three to five modeling groups are involved. MISCAN-Colon is one of the models involved in the colorectal CISNET group. Work in this thesis was conducted as part of the CISNET-project.

1.9 MISCAN-Colon

In this thesis, we have used the MISCAN-Colon microsimulation model to evaluate the effects of screening on population health. The MISCAN microsimulation model was developed at the Department of Public Health, at Erasmus MC, the Netherlands, and has been used for breast, cervical, colorectal, and prostate cancer screening. MISCAN-Colon, the CRC version of the MISCAN model, was developed in collaboration with NCI and experts in the field of CRC to assess the effect of different interventions on CRC. A graphical representation of the natural history in the model is given in Figure 1.8.

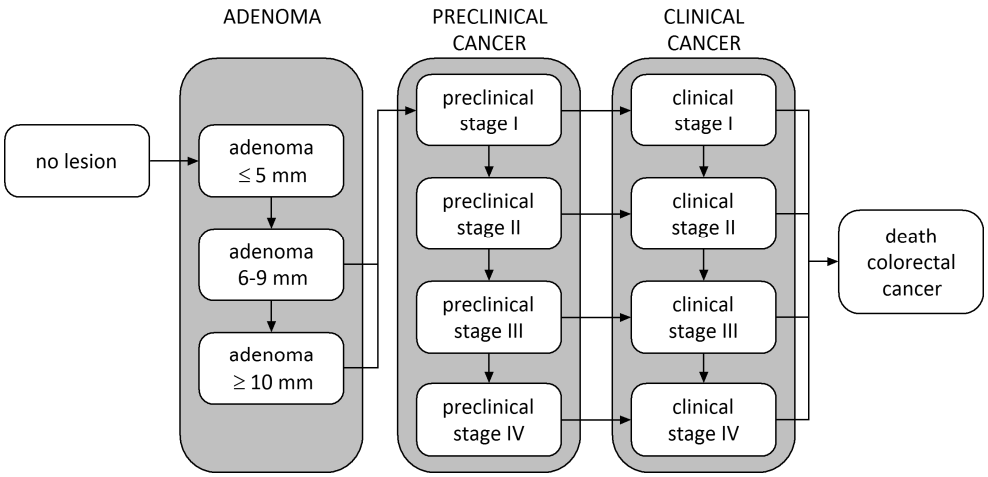

Figure 1.8: Schematic overview of the adenoma-carcinoma sequence in the MISCAN-Colon model

A detailed description of the model and the data sources that informed the quantification of the model can be found in the model appendix, in previous publications[75-77] and also in a standardized model profile.[78] In brief, the MISCAN-Colon model simulates the relevant biographies of a large population of individuals from birth to death, first without screening and subsequently with the changes that would occur in the life histories when screening would take place. CRC arises in this population according to the adenoma-carcinoma sequence.[22, 23] More than one adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (≥ 10 mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) will eventually become a clinical cancer. Diagnosis of cancer occurs on average 10 years after the manifestation of the adenoma from which it developed. This development competes with death from other causes. A preclinical cancer may progress from stage I to stage IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. The cure rate and survival after diagnosis without cure depend on the stage of the cancer.

Figure 1.9 shows an example how an individual is simulated by the model. For each individual, a time of birth and a time of death of other causes than CRC is generated, creating a life history without CRC (top line in Figure 1.9). Subsequently adenomas are simulated for that individual. For most individuals no adenomas are generated, for others multiple. In this example in Figure 1.9, the person gets one adenomas (2nd line in Figure 1.9). The adenoma arises at a certain age and grows into 6-9 mm adenoma. 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. The life history without CRC and the development of the adenoma and cancer in Figure 1.9 together lead to the life history with CRC depicted in the bottom line. Because this person dies from CRC before he dies from other causes, his death age is adjusted accordingly.

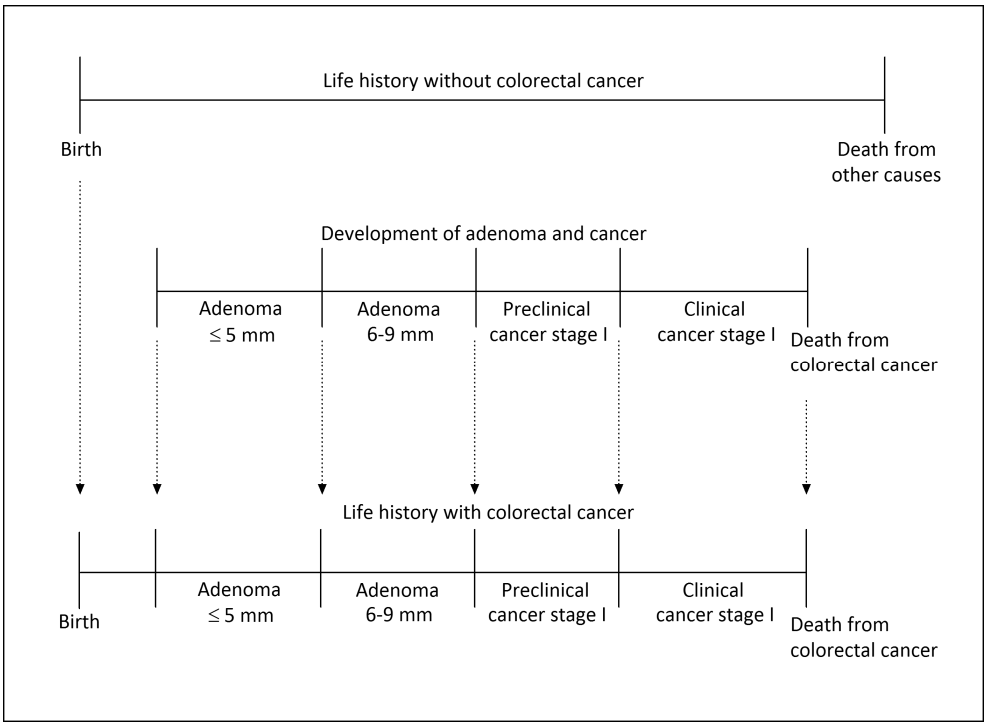

Figure 1.9: Example how an individual with development of disease is simulated in the MISCAN-Colon model

The model also simulates how screening can interrupt the development of CRC and how it improves prognosis. With screening, adenomas may be detected and removed and preclinical cancers may be found, depending on sensitivity. In this way, screening may prevent CRC incidence and/or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life expectancy of the population with and without screening.

The effect of screening on life history is explained in Figure 1.10.The top line in this figure is the life history with CRC from Figure 1.9. In this picture, there is one screening intervention. During the screening the prevalent adenoma is detected and removed. This results in a life history with CRC and screening (bottom line). From the moment of screening the adenoma is removed and this individual becomes adenoma and carcinoma free. He does not develop cancer because the precursor lesion has been removed. Therefore the person dies at the moment of death from other causes and the effect of screening is the difference in life-years in the situation without screening and the situation with screening. Of course many other possibilities could have occurred: a person could have developed new adenomas after the screening moment, or the adenoma could have been missed by the screening test, but in this case this individual really benefited from the screening intervention.

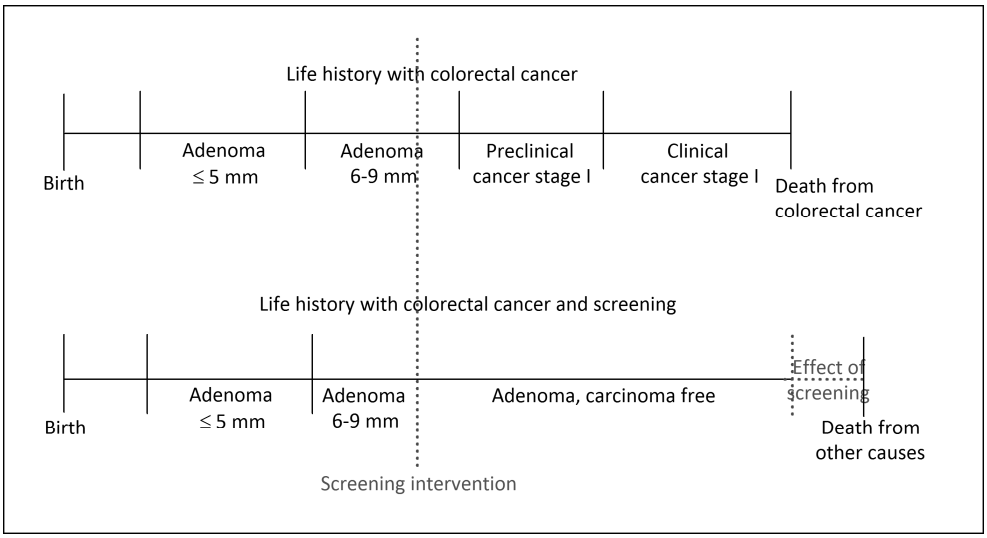

Figure 1.10: Example how screening interferes the development of CRC within the individual from Figure 1.9 in the MISCAN-Colon model

1.10 Research questions and outline of this thesis

In this thesis we have explored the effect of CRC screening on population health. More specifically we looked at the following research questions:

- Is there a colorectal cancer screening model that can explain the seemingly disparate results of the different screening trials? (Chapter 2)
- How much can current preventive and curative interventions reduce colorectal cancer mortality? (Chapter 3)
- What is the cost-effectiveness of new colorectal cancer screen tests, such as CT colonography? (Chapter 4, Chapter 8)
- Will colorectal cancer screening become cost-saving with the rapidly increasing treatment costs of colorectal cancer? (Chapter 5)
- Can individualization of screening guidelines by gender and race make colorectal cancer screening more efficient? (Chapter 6)
- What are appropriate ages and intervals for colorectal cancer screening? (Chapter 7)

Chapter 8 concludes this thesis with summary answers to and further discussion of the above research questions and directions for future research.

Chapter 2: A novel hypothesis on the sensitivity of FOBT
Results of a joint analysis of three randomized controlled trials

Abstract

Background: Estimates of the fecal occult blood test (FOBT) (Hemoccult II) sensitivity differ widely between screening trials, and will lead to divergent conclusions on the effects of FOBT screening. We used microsimulation modeling to estimate a preclinical colorectal cancer (CRC) duration and sensitivity for unrehydrated FOBT from the data of 3 randomized controlled trials of Minnesota, Nottingham and Funen. In addition to two usual hypotheses on the sensitivity of FOBT, we tested a novel hypothesis where sensitivity is linked to the stage of clinical diagnosis in the situation without screening.

Methods: We used the MISCAN-Colon microsimulation model to estimate sensitivity and duration, accounting for differences between the trials in demography, background incidence and trial design. We tested three hypotheses for FOBT sensitivity: sensitivity is the same for all preclinical CRC stages, sensitivity increases with each stage, and sensitivity is higher for the stage in which the cancer would have been diagnosed in the absence of screening than for earlier stages. Goodness-of-fit was evaluated by comparing expected and observed rates of screen-detected and interval CRC.

Results: The hypothesis with a higher sensitivity in the stage of clinical diagnosis gave the best fit. Under this hypothesis, sensitivity of FOBT was 51% in the stage of clinical diagnosis and 19% in earlier stages. The average duration of preclinical CRC was estimated at 6.7 years.

Conclusion: Our analysis corroborates a long duration of preclinical CRC, with FOBT most sensitive in the stage of clinical diagnosis.

2.1 Introduction

Colorectal cancer (CRC) is the second leading cause of cancer mortality in developed countries.[1] Because prognosis for CRC is mainly related to the extent of tumor spread at the time of diagnosis, earlier presymptomatic diagnosis offers hope of mortality reduction. Three large randomized trials have conclusively shown that screening with the Hemoccult II fecal occult blood test (FOBT) can reduce CRC mortality by 11%-33%.[28, 31, 79]

FOBT trials provide information on estimates of mortality reduction, as well as rates of screen-detected CRC, stage distribution of screen-detected CRC and interval cancers. This information can be used to obtain estimates of sensitivity of FOBT and sojourn time (i.e. the duration of the preclinical screen-detectable cancer period). Sensitivity of FOBT screening has been estimated individually for each screening trial, but these estimates differ from 54-59% for the Nottingham trial,[80] 62% for the Funen trial,[81] to 94-96% for the Minnesota trial.[82] These differences can at least partly be explained by differences in estimation methods. Using different estimates for sensitivity and how it relates to sojourn time to make predictions of CRC screening beyond the trial setting, will lead to diverging conclusions concerning the (cost-) effectiveness of FOBT screening. This not only holds for the guaiac FOBT, but also for new and more sensitive FOBTs, for which no randomized controlled trial results are available.

In this study, we used the MISCAN-Colon microsimulation model to estimate unrehydrated FOBT sensitivity and preclinical CRC duration simultaneously on the randomized controlled FOBT trials of Minnesota, Nottingham and Funen. Although, the methodology used is standard (we simulated the trials and evaluated with which values of sensitivity and duration the expected (i.e. simulated) outcomes are closest to the observed),[83, 84] the exceptionality of this analysis is that we simulated three trial populations instead of one. In addition to the usual hypotheses where FOBT sensitivity is the same for all CRC stages or increases with stage, we also evaluated a novel hypothesis where sensitivity is linked to the stage in which the cancer would have been diagnosed in the absence of screening. In the model each clinical CRC diagnosis in a certain stage is preceded by a preclinical phase in the same stage. In the novel hypothesis, we assumed that sensitivity was higher in this preclinical stage than in the earlier stages.

2.2 Material and methods

FOBT trials

Table 2.1 contains an overview of the most important differences in trial design among the Minnesota, Nottingham and Funen trials, which we accounted for.

Table 2.1: Overview of differences in design of three large FOBT screening trials*

	Minnesota	Nottingham	Funen
Period	1975-1992[†]	1981-1995	1985-2002
Trial Population	Volunteers	General population	General population
Age at entry	50-80 years	45-75 years	45-75 years
Interval	1 year or 2 years	2 years	2 years
Rounds	11 in yearly group	3-6[‡]	9[§]
Invitation schedule	All were re-invited	Only attending individuals re-invited. From 1990 all were re-invited	Only attending individuals were re-invited
Test	Unrehydrated, later rehydrated	Unrehydrated	Unrehydrated
Dietary restrictions	Yes	No	Yes
Follow-up	Mainly Colonoscopy	4 or less slides positive: re-test and eventually colonoscopy 5 or more positive: mainly colonoscopy	Colonoscopy

FOBT = fecal occult blood test.

* All three trials used 6-slide Hemoccult II FOBT.

[†] Screening was not performed in the period 1982-1986.

[‡] Results of first 5 rounds used.

[§] Results of first 8 rounds used.

The Minnesota trial was originally designed to screen and follow participants from 1975 through 1982.[85] In this period 46,551 participants ages 50 to 80 years were recruited among volunteers in Minnesota. In February 1986, screening was reinstituted and continued through February 1992. Participants were randomly assigned to screening once a year, to screening once every two years, or to a control group. Participants in the two screening groups were each asked to collect two samples from three consecutive stools on a Hemoccult II FOBT-kit. The participants were instructed to abstain from dietary factors influencing the specificity of the test. Initially, the slides were processed unrehydrated; from 1977 onwards, slides were rehydrated with a drop of deionized water to increase sensitivity. Persons with one or more slides testing positive were referred for diagnostic follow-up, mainly by colonoscopy. All persons alive without CRC were reinvited for screening after one year or two years, depending on the study arm. Controls were not invited for screening. Eighteen years after initiation, the study reported a 33% CRC mortality reduction in the annual arm and 21% in the biennial arm.[31]

From 1981 to February 1995, 152,850 subjects from the area of Nottingham were randomly allocated to biennial FOBT screening or no screening (controls).[28] Controls were not informed about the study. FOBTs were not rehydrated and dietary restrictions were imposed only for retesting

borderline results (4 or less positive slides). Screening-group participants with a positive test were offered full colonoscopy. Initially, individuals who attended screening were invited to take part in further screening every two years. From 1990 onwards, also non-attenders to screening were re-invited. After 14 years, the study reported a 15% reduction in CRC mortality in the intervention group.

From 1985 to 2002, a total of 61,933 inhabitants of Funen, Denmark ages 45 to 74 years were randomly allocated to either FOBT screening every two years or no intervention. Six-slide Hemoccult II blood tests (with similar dietary restrictions as in Minnesota but without rehydration) were sent to screening-group participants. Only participants who completed screening were invited for further rounds. Participants with positive tests were offered colonoscopy whenever possible. The reported mortality reduction in this study was 18% after seven screening rounds.[79]

MISCAN-Colon

The MISCAN-Colon microsimulation model was developed at the Department of Public Health at Erasmus MC, the Netherlands, in collaboration with the U.S. National Cancer Institute and experts in the field of CRC to assess the effect of different interventions on CRC. A graphical representation of the natural history in the model is given in Figure 1.8. A detailed description and the data sources that inform the quantification of the model can be found in the model appendix, previous studies,[75-77] and in a standardized model profile.[78] In brief, the MISCAN-Colon model simulates the relevant biographies of a large population of individuals from birth to death, first without screening and, subsequently, the changes that would occur under the implementation of screening. CRC arises in this population from the development of adenomatous polyps that may progress to carcinoma.[22, 23] More than one adenoma can occur in an individual and each can independently develop into CRC. Adenomas progress in size from small (1-5 mm) to medium (6-9 mm) to large (≥ 10 mm). Some of the adenomas eventually become malignant, transforming to a localized (Dukes A) cancer. The cancer can then progress through Dukes B and C stages to metastasized (Dukes D) cancer. In every stage there is a chance of diagnosis of the cancer because of symptoms. The survival after clinical diagnosis depends on the stage in which the cancer was detected.

After the life history of an individual in the absence of screening is generated, the model simulates if and when screening interrupts the development of CRC in that same life history. With screening, adenomas are detected and removed and cancers are detected and treated earlier in time. The probability of detection of a certain lesion depends on the sensitivity of the test for the stage the lesion is in. Because the life history in the absence of screening is first simulated, the stage in which the cancer would have been diagnosed in the absence of screening is known in the model.

The model as quantified for the general U.S. population,[75, 77] served as the basis of this analysis. The model was the same for each trial with respect to the natural history of disease and FOBT sensitivity, but differed with respect to trial-specific characteristics such as the age distribution of the eligible population, the attendance pattern and CRC risk. Table 2.2 contains an overview of model parameters that were adjusted to the trial-specifics. We assumed that differences in CRC incidence between the general U.S. population and the control groups in the three trials, were caused by differences in adenoma onset, and we adjusted the adenoma risk parameter accordingly (Table 2.2).

Also, the probability of clinical diagnosis for each CRC stage was varied between the trials, reflecting differences in stage distribution of CRC in the control groups. Screening ages, invitation protocol and compliance with screening and follow-up of positive test results were explicitly modeled in each population according to what was observed in each of the corresponding trials. As observed in the trials in first and consecutive rounds, not all invited individuals attend screening in the model. Each invited individual has a certain probability to attend first screening. For consecutive screenings, previous attenders have a higher probability to attend the consecutive screen round than non-attenders. The adenoma risk in the non-attenders was adjusted to reproduce observed CRC incidence in this group in each trial. Because, based on randomization, on average the CRC risk in the total intervention group should match that of the control group, the attenders were left with a correspondingly lower adenoma risk. Because of the difference in dietary restrictions between the trials, specificity of FOBT was allowed to vary between the three trials. With this complete set of adjustments, simulated incidence and stage distribution of the control group were within 1% of observed for all three trials (data not shown).

Table 2.2: MISCAN-Colon model parameters as adjusted specifically to the trials

Parameter	Minnesota	Nottingham	Funen
Period	1975-1981, 1987-1992	1981-1995*	1985-2000†
Birth years population	1895-1925	1906-1936	1910-1940
RR for incidence compared to U.S. population 1978	0.79	0.78	0.92
RR for incidence non-attenders versus attenders	1	1.3	1.4
Stage distribution clinically diagnosed CRC			
Dukes A	25%	13%	12%
Dukes B	34%	35%	38%
Dukes C	23%	31%	24%
Dukes D	19%	21%	26%
10-years survival by stage			
Dukes A	91%	87%	87%
Dukes B	75%	69%	69%
Dukes C	44%	43%	43%
Dukes D	1%	4%	4%
Screen interval	1 year or 2 years	2 years	2 years
Attendance to			
first screen	Age-dependent: 56-81%	63%	67%
repeat screen, if attended previously	90%	87%	93%
repeat screen, if not attended previously	42%	14%	Not re-invited: 0%
Specificity	Unrehydrated: 98%, rehydrated: 90%	99%	99%

RR = relative risk; CRC = colorectal cancer.

* Results of first 5 rounds used; † Results of first 8 rounds used.

Sensitivity hypotheses and duration

We assessed three different hypotheses for FOBT sensitivity:

- Hypothesis A: Sensitivity of FOBT is the same for all four preclinical cancer stages (one parameter).
- Hypothesis B: Sensitivity of FOBT increases with each preclinical cancer stage (four parameters).
- Hypothesis C: Sensitivity of FOBT is higher in the stage in which the cancer would have been diagnosed in the absence of screening than in earlier stages (two parameters).

Four parameters for average duration were estimated, one for each preclinical CRC stage.

In the Minnesota trial, both unrehydrated and rehydrated FOBT were used. As part of the estimation procedure, we therefore also estimated sensitivity for rehydrated FOBT assuming the same hypotheses as for unrehydrated FOBT. Because the Nottingham and Funen trials did not rehydrate tests, rehydrated FOBT was not the focus of our analysis.

Analysis

The sensitivity and duration parameters for each hypothesis were estimated by minimizing the difference between observed and expected trial outcomes. Trial outcomes used for estimation were as follows: 1) screen-detected cancers by screening round, 2) stage distribution of screen-detected cancers for first and consecutive screening rounds, and 3) interval cancers by years since negative screening. Because the trials differed in number of screening rounds and interval, the number of outcomes per trial was different. There were 26 outcomes for Minnesota, 15 for Nottingham and 18 for Funen. The corresponding expected outcomes were generated per trial with the MISCAN-Colon microsimulation model. The significance of the difference between observed and expected outcomes was assessed by the following chi-square statistic:

$$\chi_{k,i}^{\ 2} = \frac{\left(E_{k,i} - O_{k,i}\right)^2}{E_{k,i}}$$

$$E_{k,i} = Expected\ \ number\ of\ CRC\ cases\ for\ outcome\ \ i\ \ in\ trial\ k$$

$$O_{k,i} = Observed\ \ number\ of\ CRC\ cases\ for\ outcome\ \ i\ \ in\ trial\ k$$

The overall chi-square statistic of each hypothesis was calculated as the sum of the chi-square statistics of the individual outcomes. We assumed outcomes to be independent and uncorrelated. This overall chi-square statistic was minimized with an adaptation of the Nelder-and-Mead Simplex Method.[83] The Nelder-and-Mead method is a common approach to estimating parameters with microsimulation models, because derivatives of equations of these models are often too complex to use Maximum-Likelihood approaches. The resulting chi-square statistic after estimation of the parameters was a measure of the goodness-of-fit of each hypothesis. The degrees of freedom of the chi-square statistic were equal to the total number of trial outcomes compared minus the number of

parameters under the respective hypothesis. The chi-square statistics of hypotheses B and C could not be directly compared statistically because there is no hierarchical relationship between the hypotheses. We used the Akaike Information Criterion to compare these two hypotheses. We assumed the outcomes were Poisson distributed. The formula for the Akaike Information Criterion with Poisson distributed outcomes is:

$$AIC = 2 \cdot n - 2 \cdot \sum_{i,k} \left(E_{k,i} \cdot \ln\left(O_{k,i}\right) - O_{k,i} \right)$$

$$n = Number\ of\ parameters$$

$$E_{k,i} = Observed\ number\ of\ CRC\ cases\ for\ outcome\ i\ in\ trial\ k$$

$$O_{k,i} = Expected\ number\ of\ CRC\ cases\ for\ outcome\ i\ in\ trial\ k$$

The Akaike Information Criterion is a standard tool for model selection, with the model having the lowest value being the best.

We also derived conditional confidence intervals around the estimated parameters. We determined to what values we could change each of the estimated parameters without significantly worsening the goodness-of-fit of the model. The values closest to the estimated parameter at which the goodness-of-fit of the model significantly worsened (p=0.05) constituted the boundaries of the confidence interval.

2.3 Results

Sensitivity and duration

Table 2.3 shows the estimates for sensitivity and duration. Assuming the same sensitivity of FOBT for all preclinical CRC stages, resulted in shorter duration of Dukes A and B (1.6 and 2.1 years) than in Dukes C and D (4.0 and 3.2 years), due to higher detection rates in later stages than in earlier ones. With these durations it took on average 6.0 years for a preclinical cancer to become clinically diagnosed. The estimated sensitivity of FOBT under this hypothesis was 33%. Assuming a higher sensitivity of FOBT with each Dukes stage resulted in a longer duration for Dukes A and C (3.8 and 3.6 years, respectively) compared to Dukes B and D (2.4 and 2.1 years). The average duration of preclinical CRC was 8.0 years. The sensitivity of FOBT is comparable for Dukes B and C disease (35-38%), and lower for Dukes A (13%) and higher for Dukes D (66%). Assuming a higher sensitivity of FOBT in the stage of clinical diagnosis, Dukes C has longer duration (3.7 years) than the other three stages (2.5 years for Dukes A and B and 1.5 years for Dukes D). The average duration of preclinical CRC is 6.7 years. Sensitivity is considerably higher in stage of clinical diagnosis than in earlier stages (51% versus 19%).

Table 2.3: Estimated values (confidence interval) for sensitivity of FOBT and duration of preclinical CRC for three sensitivity hypotheses

Parameters	Hypothesis A	Hypothesis B	Hypothesis C
Average duration in years			
Dukes A	1.6 (1.4-1.8)	3.8 (3.3-4.2)	2.5 (2.3-2.8)
Dukes B	2.1 (1.9-2.5)	2.4 (2.1-2.7)	2.5 (2.2-3.0)
Dukes C	4.0 (3.2-4.6)	3.6 (3.0-4.3)	3.7 (3.1-4.7)
Dukes D	3.2 (2.2-4.3)	2.1 (1.4-2.8)	1.5 (1.2-2.7)
Total*	6.0 (5.2-6.9)	8.0 (7.1-9.0)	6.7 (5.8-7.7)
Sensitivity unrehydrated FOBT (%):†			
Dukes A	33 (30-37)	13 (12-16)	
Dukes B	33 (30-37)	35 (33-42)	
Dukes C	33 (30-37)	38 (36-44)	
Dukes D	33 (30-37)	66 (61-76)	
Stage of clinical diagnosis			51 (47-65)
Earlier stages			19 (16-25)

FOBT = fecal occult blood test; CRC = colorectal cancer.
Hypothesis A: same sensitivity of FOBT for all cancer stages.
Hypothesis B: sensitivity increases with each cancer stage.
Hypothesis C: sensitivity of FOBT higher in stage of clinical diagnosis.
* Calculated as (% in stage A * duration A) + (% in stage B * duration A+B) + (% in stage C * duration A+B+C) + (% in stage D * duration A+B+C+D).
† For the Minnesota trial sensitivities of rehydrated FOBT were as follows: 28% for Hypothesis A; 10% Dukes A, 26% Dukes B, 56% Dukes C and 63% Dukes D for Hypothesis B; 55% stage of clinical diagnosis, 10% earlier stages for Hypothesis C.

Goodness-of-fit

Comparison of aggregated trial results

Table 2.4 shows observed and expected detection and interval cancer rates aggregated for the three FOBT trials and the associated goodness-of-fit for each hypothesis.

Table 2.4: Observed and expected screen-detected CRC, stage distribution of screen-detected cancers by phase for first and consecutive rounds and interval cancers and chi-square statistic for three hypotheses for FOBT sensitivity, three trials aggregated

Outcome	Observed	Expected		
		Hypothesis A 6 parameters	Hypothesis B 12 parameters	Hypothesis C 8 parameters
Screen-detected CRC, round 1				
Cases (rate per 1000 persons screened)	247 (2.21)	256 (2.29)	252 (2.25)	256 (2.29)
Cases (%) Dukes A	116 (48)	91 (38)*	93 (39)†	101 (42)
Cases (%) Dukes B	60 (25)	76 (32)	69 (29)	76 (32)
Cases (%) Dukes C	52 (22)	59 (24)	62 (26)	53 (22)
Cases (%) Dukes D	12 (5)	14 (6)	17 (7)	11 (5)
Screen-detected CRC, consecutive rounds				
Cases (rate per 1000 persons screened)	492 (1.56)	531 (1.68)	543 (1.72)†	522 (1.66)
Cases (%) Dukes A	178 (39)	204 (45)	205 (45)	202 (44)
Cases (%) Dukes B	157 (34)	137 (30)	132 (29)†	142 (31)
Cases (%) Dukes C	98 (21)	94 (21)	100 (22)	92 (20)
Cases (%) Dukes D	25 (5)	23 (5)	21 (5)	22 (5)
Interval cancers in first two years after screening (rate per 1000 person years)	369 (0.73)	432 (0.85)*	419 (0.82)†	386 (0.76)
Chi-square statistic‡		83*	77*	73†
Akaike Information Criterion‡		-10,569	-10,562	-10,582

CRC = colorectal cancer; FOBT = fecal occult blood test.
Hypothesis A: Same sensitivity for all cancer stages.
Hypothesis B: Sensitivity increases with each cancer stage.
Hypothesis C: Sensitivity is higher in stage of clinical diagnosis.
* Expected outcome significantly different from observed ($p < 0.01$).
† Expected outcome significantly different from observed ($p < 0.05$).
‡ Based on 59 trial specific outcomes.

For hypothesis A, the expected outcomes differed significantly from observed (p<0.01). This was mainly due to a significantly lower number of expected screen-detected cancers in Dukes A (first round, 91 expected vs. 116 observed), and a significantly higher rate of interval cancers in the first two years after screening (432 expected versus 369 observed). For hypothesis B, the expected outcomes also differed significantly from observed (p<0.01). Four expected outcomes under this hypothesis were different from observed: as with hypothesis A, the expected number of first round screen-detected cancer cases in Dukes A was lower than observed (93 vs. 116) and the number of interval cancers was higher than observed (419 vs. 369). Moreover, the observed number of screen-detected cancer cases in consecutive screen rounds was 543, where 492 were expected and the observed cases in stage B were 157, where 132 were expected. Hypothesis C had the lowest chi-square statistic (χ^2_{51} = 73) (Table 2.4). Although none of the expected outcomes aggregated over the three trials differed significantly from observed under hypothesis C, summed together the outcomes significantly differed (p=0.02). Nonetheless, hypothesis C was significantly better than hypothesis A (p<0.01), whereas hypothesis B was not significantly better than hypothesis A (p=0.48). Finally, hypothesis C had a better goodness-of-fit than hypothesis B with fewer parameters. This finding also showed from the Akaike Information Criterion, which was -10,582 for hypothesis C, better than the -10,562 for hypothesis B.

Comparison of detailed trial specific results (results not shown)

Under hypothesis C, five expected trial-specific outcomes differed significantly from observed: the expected interval cancer rate in the first year after screening in the Minnesota trial; the expected number of screen-detected cases in the first screening round in the Nottingham trial; and the number of screen-detected cases in the first screening round, the number of screen-detected cases in the second round and the percentage of screen-detected cases in Dukes B in the Funen trial. In addition to these outcomes, there were three other significant differences under hypotheses A and B: the expected rate of interval cancers in the second year after screening in the Minnesota trial; the interval cancers after the first screening round in the Nottingham trial; and the screen-detected cancers in the seventh round in the Funen trial.

2.4 Discussion

We have fitted sensitivity and duration for three different sensitivity models to the Minnesota, Nottingham and Funen trial results. We found that the hypothesis in which sensitivity of FOBT is highest in the stage in which the cancer would have been clinically diagnosed in the absence of screening gave the best fit, with an estimate of 51%. In earlier stages, estimated sensitivity was 19%. The mean preclinical CRC duration was estimated at 6.7 years.

The hypothesis that sensitivity of FOBT is highest in the stage of clinical diagnosis was best for three reasons. First, it gave the best statistical fit to observed trial outcomes (although differences in goodness-of-fit between the hypotheses are small). Second, it is also biologically the most plausible one, because tumor-bleeding resulting in (macroscopic) detection of blood in stool is often the symptom leading to clinical detection of CRC. About 34% to 58% of CRC present with rectal

bleeding.[86-89] It is very plausible that occult bleeding precedes macroscopic bleeding and, thus, that sensitivity of FOBT depends on time to clinical diagnosis. Interestingly the range of cancers that present with bleeding compares well with our sensitivity estimate of 51%. Third, this hypothesis is able to explain the discrepancy between the high FOBT sensitivity estimates based on trial results (54%-96%)[80-82] and the low estimates based on back-to-back studies with colonoscopy (11-50%).[36, 90-94] With a 1-2 year screening interval, trials mainly estimate sensitivity in the last phase of cancer progression, i.e. the stage before diagnosis in the absence of screening. Our sensitivity estimate of 51% for this phase, is in line with the individual estimates by the investigators of the Nottingham and Funen trials.[80, 81] Colonoscopy is sensitive for all stages of CRC and showed that FOBT detects a much smaller proportion of all CRC. The weighted average of our sensitivity in stage of clinical diagnosis and our sensitivity in earlier stages of 32% is in line with that observation.

In all three trials the observed stage distribution in repeat screening rounds is less favorable than the stage distribution in the first screening round, while for all three hypotheses this is predicted to be the other way around. This discrepancy can be explained by assuming the presence of occult bleeding indolent cancers (i.e. early-stage cancers never progressing or giving symptoms), especially in stage A. These indolent cancers would be detected during first screening, allowing for many early stage cancers in the first screening round. At consecutive screening rounds, these cancers would no longer be present, so that then fewer early-stage cancers are detected. This would be adding a considerable amount of length-biased sampling. With the current assumption of an exponential distribution, there already is a considerable variability in the duration of CRC and, therefore, amount of length-biased sampling accounted for in the model, but modeling indolent cancers would further increase length-biased sampling. This would potentially further improve the fit of the model, not only for the favorable stage distribution in first screenings but potentially also regarding the sensitivity of rehydrated FOBT. Currently, our estimate for rehydrated FOBT in stages before the stage of clinical detection is lower than for unrehydrated FOBT. Several studies have shown that rehydration of FOBT slides increases sensitivity.[85, 95-98] Rehydration of FOBT slides was mainly done in the second phase of the Minnesota trial with only follow-up screening rounds. Because the modeled detection rates in follow-up rounds, and thus in this phase, are higher than observed, the estimated sensitivity for rehydrated FOBT needed to be low to compensate. With indolent cancers, the detection rates at consecutive screenings would be lower and, consequently, the estimate for rehydrated FOBT sensitivity higher.

Dividing FOBT sensitivity in a phase with low sensitivity and a phase with high sensitivity is a novel way of describing the occult blood detection process. Despite its plausibility, this hypothesis was never tested, maybe because it cannot be observed in studies (time of clinical manifestation of a disease is not known), or estimated through classic sensitivity estimation. With microsimulation, time of clinical manifestation is pseudo-observed and, therefore, sensitivity of the test can be varied accordingly. But up to now, microsimulation models have assigned a certain sensitivity of FOBT for preclinical CRC stages, regardless of when individual cancers become clinical.[72] In these models, sensitivity was not varied at all between stages (our hypothesis A).

Our improved estimates can be used to better extrapolate the trial results to newer and more sensitive FOBTs, for which no randomized controlled trial results are available. Because these tests have higher sensitivity, one could argue that the screening interval could be lengthened with these tests. However, the mechanism of detection of occult blood is the same for these tests, so it is likely

that these more sensitive tests are also mainly sensitive for lesions shortly before clinical diagnosis. Therefore also with a higher sensitivity, it will remain important to screen with FOBT frequently. Our results also have implications for endoscopy screening. Although the attention of endoscopy is often on detection and treatment of precancerous adenomas, the effectiveness due to detection of cancers in an (very) early stage is stressed by this analysis. A longer preclinical CRC duration improves the efficacy of endoscopy screening. All together, the improved model will be more fitted to compare (newer) FOBT testing to endoscopy screening. To test the 6.7 years dwell time for preclinical cancer as estimated here, the CRC detection rates of endoscopy together with incidence in the control group are required.

In conclusion, the results of the Minnesota, Nottingham and Funen trials were best explained by the hypothesis that FOBT becomes more sensitive shortly before clinical diagnosis. The total preclinical cancer duration was estimated to be as long as 6.7 years. FOBT has only 20% sensitivity for the majority of this period. Only for cancers in the stage in which the cancer would have been diagnosed in the absence of screening (on average the last 2.5 years before diagnosis), sensitivity becomes 50%.

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Chapter 3: How much can current interventions reduce colorectal cancer mortality in the U.S.?

Mortality projections for scenarios of risk factor modification, screening, and treatment

Abstract

Background: Although colorectal cancer (CRC) is the second leading cause of cancer death in the U.S., available interventions to reduce CRC mortality are disseminated only partially throughout the population. This study assessed the potential reduction in CRC mortality that may be achieved through further dissemination of current interventions for risk factor modification, screening, and treatment.

Methods: The MISCAN-Colon microsimulation model was used to simulate the 2000 U.S. population with respect to CRC risk factor prevalence, screening use, and treatment use. The model was used to project age-standardized CRC mortality from 2000 to 2020 for 3 intervention scenarios.

Results: Without changes in risk factor prevalence, screening use, and treatment use after 2000, CRC mortality would decrease by 17% by the Year 2020. If the 1995 to 2000 trends continue, then the projected reduction in mortality would be 36%. However, if trends in the prevalence of risk factors could be improved above continued trends, if screening use increased to 70% of the target population, and if the use of chemotherapy increased among all age groups, then a 49% reduction would be possible. Screening drove most (23%) of the projected mortality reduction with these optimistic trends; however, decreasing risk factors (16%) and increasing use of chemotherapy (10%) also contributed substantially. The contribution of risk factors may have been overestimated, because effect estimates could not be obtained from randomized controlled trials.

Conclusion: Currently available interventions for risk factor modification, screening, and treatment have the potential to reduce CRC mortality by almost 50% by the Year 2020. However, without action now to further increase the uptake of current effective interventions, the reduction in CRC mortality may be only 17%.

3.1 Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in the U.S. For 2006, it is estimated that there will be 148,610 patients with newly diagnosed CRC and 55,170 deaths from CRC.[99] The Healthy People Consortium and the American Cancer Society (ACS) recognize the burden of CRC and have recommended the objective of reducing CRC mortality by 34% in 2010[100] and by 50% in 2015,[101] respectively. CRC deaths can be prevented. Seventy percent of colon cancers in a cohort of middle-aged men in the U.S. potentially would be preventable by modifying risk factor behavior, such as smoking and alcohol use.[102] Fecal occult blood testing (FOBT) may decrease CRC mortality by 15% to 33%.[28, 29, 31] Sigmoidoscopy reduced CRC mortality by 60% within the reach of the sigmoidoscope in case-control studies.[45, 46] Recent breakthroughs in treatment have lengthened the median survival of patients diagnosed with metastatic CRC from 6 months (without any chemotherapy) to 20 months (with cytotoxic and targeted chemotherapy).[103] Similar improvements have been reported for patients with earlier stage disease.[104] However, these interventions are disseminated only partially throughout the population. Obesity prevalence is currently 30% in the U.S. and is still increasing.[105] Despite recommendations of the ACS[106] and the U.S. Multisociety Task Force on CRC,[107] national data on CRC screening uptake show that only 47% of men and 43% of women age 50 years and older reported having either an FOBT within the past year, a sigmoidoscopy within the past 5 years, or a colonoscopy within the past 10 years.[108] Chemotherapy rates decline dramatically with chronologic age,[109] although a pooled analysis showed attenuated but still significant benefits of chemotherapy in elderly patients.[110] The objective of the current study was to assess the extent to which greater dissemination of current interventions for risk factor modification, screening, and treatment can reduce CRC mortality in the general U.S. population.

3.2 Materials and methods

MISCAN-Colon microsimulation model

The Department of Public Health at Erasmus MC, the Netherlands, developed the MISCAN-Colon microsimulation model in collaboration with the U.S. National Cancer Institute (NCI) to assess the effect of different interventions on CRC. The MISCAN-Colon model simulates a large population of individuals in whom CRC can arise according to the adenoma-carcinoma sequence.[22, 23] More than 1 adenoma can occur in an individual, and each adenoma can develop independently into CRC. Adenomas progress in size from small (1-5 mm), to medium (6-9 mm), to large (≥10 mm). Some adenomas eventually become malignant, transforming into stage I cancer. The cancer then progresses from stage I to stage IV. In every stage, there is a chance of detecting the cancer because of symptoms. Survival after clinical detection depends on the stage in which the cancer is detected. The MISCAN-Colon model has been described previously in great detail.[76-78] In the model, we distinguish 3 types of interventions: risk factor modification, screening, and treatment.

Risk factor modification

In the MISCAN-Colon model, risk factor behavior influences the incidence of adenomas. We included the established risk factors for CRC of smoking, obesity, and red meat consumption as well as aspirin use, supplemental folate use, and physical activity. The odds ratios, which were estimated from 2 long-term cohort studies (The Health Professionals Follow-Up Study and the Nurses Health Study)[10-15, 17, 18, 111] and from the studies by Jacobs et al.[16] and Rosenberg et al.,[19] were used as approximations of the relative risks for adenoma incidence (Table 3.1) and were assumed to be multiplicative.

Table 3.1: Risk factors for colorectal carcinoma in the MISCAN-Colon microsimulation model: categories of exposure and assumed relative risks for developing colorectal adenomas

Risk Factor	Categories	RR for adenomas	Reference(s)
Smoking	Smoker 15 years ago vs. nonsmoker 15 years ago	1.8	Giovannucci et al., 1994[12, 13]
Obesity	Body mass index ≥30 kg/m^2 vs. <30 kg/m^2	1.5	Giovannucci et al., 1995[10] and 1996[11]
Red Meat consumption	≥2 Times per week vs. less	1.4	Giovannucci et al., 1994[111]
Physical Activity	Level of physical activity according to current CDC guideline vs. not*	0.6	Giovannucci et al., 1995[10] and 1996[11]
Folate	Multivitamin use ≥4 times per week vs. less	0.7	Giovannucci et al., 1993[15] and 1998;[14] and Jacobs et al., 2003[16]
Aspirin	≥4 Times per week vs. less	0.5	Giovannucci et al., 1995;[18] Chan et al., 2004;[17] Rosenberg et al., 1991[19]

RR = relative risk; CDC = Centers for Disease Control and Prevention.
*CDC guideline: ≥30 minutes of moderate physical activity ≥5 days per week or ≥20 minutes of vigorous physical activity ≥3 days per week.

For smoking, recent studies have suggested that the induction period for CRC risk is from 35 years to 40 years.[112, 113] Consequently, we required data for the prevalence of risk factors from as early as 1965. Data were obtained from the Cancer Progress Report.[105] Additional age-specific data were obtained directly from its underlying resources: the National Health Interview Survey (NHIS),[114] the National Health and Nutrition Examination Survey,[115] and the Behavioral Risk Factors Surveillance System.[116] For years in which data were not available, trends were extrapolated linearly. For modeling purposes, we assumed that the prevalence of risk factors was not associated (see Table 3.2 for risk factor prevalence from 1965 to 2000).

Table 3.2: Age-adjusted risk factor prevalence, screening dissemination and treatment use for colorectal carcinoma in the MISCAN-Colon microsimulation model for selected years from 1965 to 2000

Year:	1965	1970	1975	1980	1985	1990	1995	2000
Risk Factors								
Smoking (% adult current smokers)	42	37	36	33	30	26	25	23
Obesity (% adults obese)	13	13	14	14	17	21	25	31
Red meat (% adults consuming ≥2 times per week)	97	97	95	93	89	85	81	78
Physical activity (% adults adhering to guidelines)	25	25	25	25	25	24	25	26
Multivitamin (% adult-users)	0	0	5	12	20	27	34	38
Aspirin (% adult-users)	5	5	5	5	6	8	9	10
Screening								
Home-based FOBT (% adults age ≥50 years with home-based FOBT in past two years)	0	0	0	5	14	18	21	24
Endoscopy (% adults age ≥50 years ever had endoscopy)	0	0	0	8	21	30	35	39
Treatment								
Rate of adjuvant chemotherapy for stage III	0	0	1	12	37	69	73	73
5-FU based regimens without other agents*	0	0	1	12	37	69	73	73
Infusional 5-FU and oxaliplatin	0	0	0	0	0	0	0	0
Rate of chemotherapy for metastatic disease	0	13	25	27	49	59	66	66
5-FU based regimens*	0	13	25	27	49	59	20	20
5-FU and irinotecan	0	0	0	0	0	0	46	46
5-FU, irinotecan and oxaliplatin	0	0	0	0	0	0	0	0
5-FU irinotecan, oxaliplatin, and the biologics (cetuximab and bevacizumab)	0	0	0	0	0	0	0	0

5-FU = 5-fluorouracil; FOBT = fecal occult blood test.

* Includes regimens with 5-FU potentiating agents like leucovorin and levamisole.

Screening

Screening and surveillance lead either to the removal of an adenoma and prevention of CRC or to the early detection of a carcinoma, possibly improving prognosis. We considered screening with FOBT and endoscopy (including flexible sigmoidoscopy and colonoscopy). Based on our prior work (see Loeve et al.)[76, 77] and other studies,[81, 117, 118] we assumed the performance parameters of the screening tests that are shown in Table 3.3. NHIS provided rates for ever being screened and time since last screening by 5-year age groups in 1987, 1992, 1998, and 2000. We assumed no screening prior to 1978. The screening rates between data points were estimated by linear extrapolation (see Table 3.2). Because of the poor performance characteristics of office-based FOBT,[90] we accounted only for home-based FOBT. Because NHIS did not distinguish between home-based and office-based FOBTs before 2000, we estimated that the percentage of home-based FOBTs for earlier years would be the same as it was in 2000.

Table 3.3: Characteristics of home-based fecal occult blood testing, sigmoidoscopy, and colonoscopy in the MISCAN-Colon microsimulation model: sensitivity for small, medium, and large adenomas and cancers; specificity; and segments screened

Parameter	Home-based FOBT*	Sigmoidoscopy†	Colonoscopy‡
Sensitivity (%)			
Small adenomas (1-5 mm)	2	75	80
Medium adenomas (6-9 mm)	2	85	85
Large adenomas (≥10 mm)	5	95	95
Cancers	60	95	95
Specificity (%)	98	95§	90§
Segments screened‖	Whole colon and rectum	75% reach descending colon, none reach beyond splenic flexure	95% reach ascending colon, 70% reach cecum

FOBT = fecal occult blood test.

* See Gyrd-Hansen et al., 1997.[81]

† See Loeve et al., 2000;[77] Hixson et al., 1991;[117] and Rex et al., 1997.[118]

‡ See Hixson et al., 1991[117] and Rex et al., 1997.[118]

§ Lack of specificity of sigmoidoscopy and colonoscopy is because of detection and removal of non-adenomatous polyps.

‖ Only adenomas and cancers within the reach of a screening test can be detected. Sensitivity applies to adenomas and cancers within reach of the test.

Treatment

In the last 20 years, improvements to systemic CRC chemotherapy have increased the cure rate of locally advanced disease and prolonged the survival for patients with advanced disease. In the model, we distinguished 4 chemotherapy regimens, depending on the treatment strategies available to patients in the U.S. who were diagnosed in a particular time period. They were: 1) 5-fluorouracil, which was available before 1996; 2) 5-fluorouracil and irinotecan (1996-2001); 3) 5-fluorouracil, irinotecan, and oxaliplatin (2002-2003); and, 4) 5-fluorouracil, irinotecan, oxaliplatin, and bevacizumab/cetuximab (2004 onward). The efficacy of each of these treatment regimens was estimated by using the hazard ratios for disease-free survival from published clinical trials[104, 119-130] that were applied to the stage-specific relative survival rates for 1975 to 1979 from the Surveillance, Epidemiology and End Results (SEER) Program. Hazard ratios for disease-free survival for elderly patients were attenuated modestly based on a meta-analysis of elderly adjuvant colon cancer chemotherapy trial participants[110] and on survival outcomes with and without adjuvant treatment in SEER-Medicare.[131, 132] Table 3.4 provides a summary of the hazard ratios for the various chemotherapy strategies compared to a referent category of treatment without chemotherapy.

To estimate chemotherapy use by age and time period in the U.S. population, we used the SEER-Medicare linked data base.[131, 132] This provided approximate treatment histories through 2002 for the population age 65 years and older who were diagnosed with CRC from 1991 to 1999. For the population younger than age 65 years, we used survey data and patterns-of-care studies.[133, 134] For utilization patterns prior to 2000, estimates are available in Table 3.2.

Table 3.4: Hazard ratios of dying from colorectal carcinoma for various chemotherapy treatment regimens compared to no adjuvant chemotherapy in the MISCAN-Colon microsimulation model

Chemotherapy treatment regimens*	Hazard ratio			
	Adjuvant therapy for stage III disease		Therapy for metastatic disease	
	Age <75 years	Age ≥ 75 years[†]	Age <75 years	Age ≥ 75 years[†]
One cytotoxic agent (5-FU)[‡]	0.74[§]	0.82	0.70[||]	0.80
Two cytotoxic agents (5-FU and irinotecan)	n.a.[v]	n.a.[v]	0.60**	0.70
Three cytotoxic agents (5-FU, irinotecan, and oxaliplatin)	0.61[††]	0.71	0.50[‡‡]	0.60
Three cytotoxic agents and effective biologic therapy (5-FU, irinotecan, and oxaliplatin with bevacizumab/cetuximab)	n.a.[§§]	n.a.[§§]	0.42[|||]	0.46

5-FU = 5-fluorouracil; n.a. = not applicable.

*Chemotherapy treatment regimens refer to the agents available for the treatment of colorectal carcinoma during a particular period.

[†] See Sargent et al., 2001.[110]

[‡] Includes regimens with 5-FU potentiating agents like leucovorin and levamisole.

[§] See Gill et al., 2004.[123]

[||] See Saltz et al., 2000[129] and de Gramont et al., 2000.[122]

[v] 5-FU and irinotecan were identified as ineffective for adjuvant therapy in a large United States randomized trial (Saltz et al., 2004)[128].

** See Saltz et al., 2000.[129]

[††] See Andre et al., 2004.[104]

[‡‡] See de Gramont et al., 2000;[122] Goldberg et al., 2004;[124] and Tournigand et al., 2004.[130]

[§§] Adjuvant treatment trials of cytotoxic therapy plus biologic agents are just underway with no data yet available. Accordingly, the potential benefit of adding biologic therapy to adjuvant regimens was not considered.

[|||] See Hurwitz et al., 2004[125] and Cunningham et al., 2004.[121]

Model calibration and validation

Accounting for the risk factor dissemination before 1975 and the stage-specific survival rates from 1975 to 1979, the MISCAN-Colon model was calibrated to reproduce the 1975 to 1979 age-specific CRC incidence rates,[135] which were representative of the U.S. population prior to screening. Subsequently, we added trends in risk factor prevalence and screening and treatment use from 1975 to 2000 to generate a population with the characteristics of the 2000 U.S. population. Model predictions for CRC incidence and mortality until 2000 all were within 6% of the observed incidence and mortality.

Scenarios

We considered 3 different hypothetical scenarios to project CRC mortality between 2000 and 2020.

The frozen-2000 scenario

Risk factor prevalence and the use of screening and treatment remain at the levels observed in the Year 2000.

The continued-trends scenario

Observed trends in risk factors and screening from 1995 to 2000 continue at the current rates up until 2020. Recently approved treatment strategies are adopted rapidly, as illustrated in Table 3.5.

The optimistic-trends scenario

This scenario considers continued trends through 2004. From 2005 onward, the model assumes that risk factor prevalence in the U.S. population improves by 4% per year (obesity stabilizes at its 2005 level, and aspirin was not considered a possible intervention because of adverse effects of bleeding)[136]. CRC screening rates reach current levels of breast cancer screening (70%) by 2010, and all patients who are eligible for chemotherapy (those without significant comorbidities) receive the best currently available chemotherapy from 2005 onward. For this scenario we also estimated the contributions of risk factor modification and increased use of screening and treatment separately on the reduction of CRC mortality.

The projected levels of risk factor prevalence and screening and treatment use in 2020 associated with each of the scenarios described above are summarized in Table 3.5. Output was age-standardized to the U.S. 2000 standard population.[137]

Table 3.5 Levels of risk factor prevalence, screening use, and treatment use in 2020 by scenario in the MISCAN-Colon microsimulation model

Scenario:	Frozen-2000	Continued-trends	Optimistic-trends
Risk Factors			
Smoking (% adult current smokers)	23	17	11
Obesity (% adults obese)	31	45	34
Red meat (% adults consuming ≥2 times per week)	78	69	41
Physical activity (% adults adhering to guidelines)	26	34	51
Multivitamin (% adult-users)	38	55	76
Aspirin (% adult-users)	10	15	15*
Screening			
Home-based FOBT (% adults age ≥50 years with home-based FOBT in past two years)	24	35	38
Endoscopy (% adults age ≥50 years ever had endoscopy)[†]	39	56	61
Treatment			
Rate of adjuvant chemotherapy for stage III	73	76	84
5-FU based regimens without other agents	73	27	0
Infusional 5-FU and oxaliplatin	0	49	84
Rate of chemotherapy for metastatic disease	66	70	83
5-FU based regimens	20	6	0
5-FU and irinotecan	46	1	0
5-FU, irinotecan and oxaliplatin	0	18	0
5-FU irinotecan, oxaliplatin, and the biologics (cetuximab and bevacizumab)	0	45	83

5-FU = 5-fluorouracil; FOBT = fecal occult blood test.

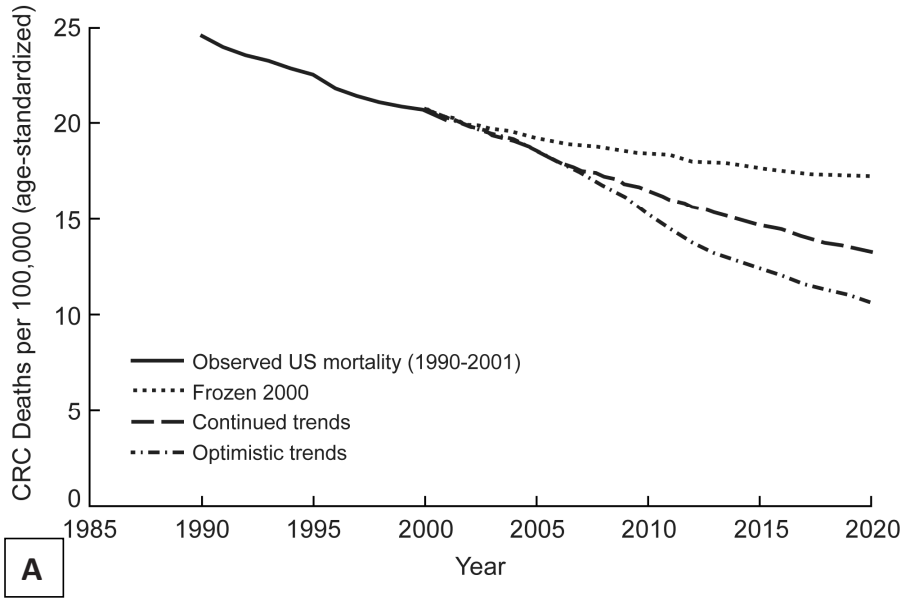
* Because of adverse effects of bleeding (see Imperiale, 2003)[136], aspirin was not considered a possible intervention.

[†] Endoscopy utilization includes 65% of procedures by colonoscopy (including colonoscopies for surveillance and for diagnostic follow-up of positive FOBTs and sigmoidoscopies) and 35% of procedures by sigmoidoscopy.

3.3 Results

Without further changes in risk factor prevalence, screening use, and treatment use after 2000, the MISCAN-Colon model predicted that the CRC mortality rate per 100,000 population would decline from 20.8 in 2000, to 18.4 in 2010, and to 17.3 in 2020 (frozen-2000 trends) (Fig. 3.1A). CRC mortality was reduced by 11% between 2000 and 2010, and the mortality reduction leveled off at 17% by 2020. If the 1995 to 2000 trends continue, then MISCAN-Colon predicted mortality rates of 16.5 per 100,000 population in 2010 and 13.3 per 100,000 population in 2020 (continued-trends) (Fig. 3.1A), representing a 21% reduction by 2010 and a 36% reduction by 2020 compared to 2000. With more optimistic trends, mortality rates of 15.3 per 100,000 population in 2010 and 10.7 per100,000 population in 2020 were achieved, representing mortality reductions of 26% by 2010 and 49% by 2020 (optimistic-trends) (Fig. 3.1A).

Figure 3.1B shows the separate effects of risk factor modification, increased screening use, and increased treatment use on reducing CRC mortality in the optimistic-trends scenario. The frozen-2000 scenario was used as a referent point for additional mortality reduction. In 2010, screening achieved a CRC mortality of 16.6 per 100,000 population—a 9% additional mortality reduction over the 11% mortality reduction of the frozen-2000 scenario. The additional mortality reduction obtained through treatment is 6% with a CRC mortality of 17.2 per 100,000 population. The effect of risk factor modification in the short-term was much smaller, an additional 1% reduction (CRC mortality of 18.1 per 100,000 population) over the frozen-2000 scenario. Over the 20-year period, however, risk factor modification had a large impact, achieving an additional 12% mortality reduction beyond the estimate for the frozen-2000 scenario. The long-term additional CRC mortality reductions that were generated by increased screening use and increased treatment use were 17% and 7%, respectively.



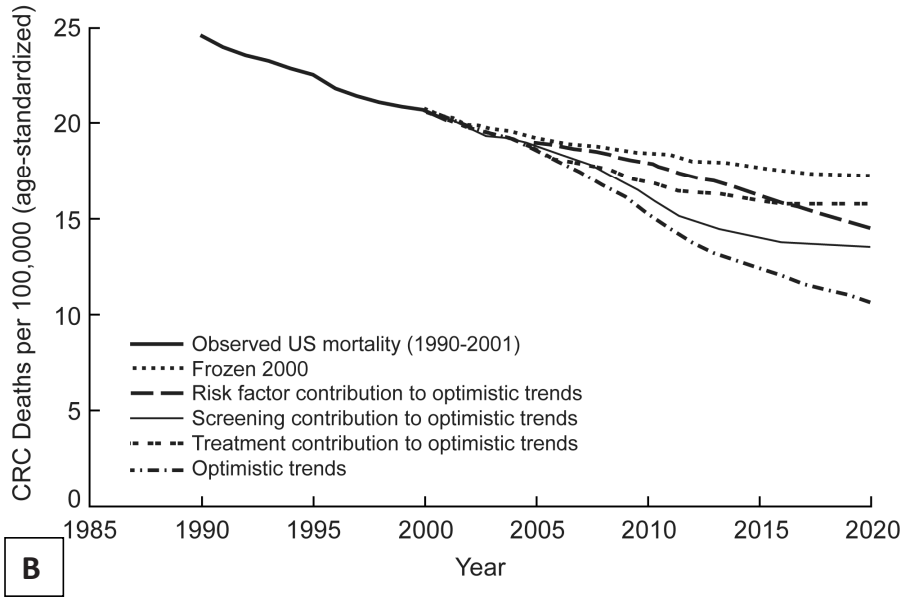


Figure 3.1: (A) Age-standardized colorectal cancer (CRC) mortality rates until 2001 are shown as observed (National Center for Health Statistics, 2001)[138] and from 2000 onward, as simulated by the frozen-2000, continued-trends, and optimistic-trends scenarios (2000-2020). (B) Age-standardized CRC mortality rates until 2001 as observed (National Center for Health Statistics, 2001)[138] and from 2000 onward, as simulated by the frozen-2000 and the optimistic-trends scenarios overall and with the separate contributions of risk factor modification, increasing screening use and increasing treatment use for the optimistic-trends scenario.

3.4 Discussion

The potential for reducing CRC mortality with currently available interventions is considerable. With a yearly 4% decrease in the prevalence of risk factors, an increase in CRC screening to 70%, and widespread use of the best available chemotherapy across all age groups, we estimate a 49% CRC mortality reduction by the Year 2020. The mortality reduction will be smaller if current trends continue (36% reduction) or if no further changes occur in the underlying contributors to CRC mortality (17% reduction). Of the 3 types of interventions considered, increasing screening has the largest effect on CRC mortality both after 10 years and after 20 years. Widespread use of currently available chemotherapy has an immediate effect on CRC mortality, but its effect ranks third by 2020. Risk factor modification would take the longest to show an effect on CRC mortality but would provide an effect comparable to screening by the Year 2020.

Microsimulation is a powerful tool for assessing the benefit of different types of interventions simultaneously on a population level. Like all projections, uncertainty exists in underlying data and assumptions; therefore, the results should be interpreted with some caution. Given the lack of randomized controlled trials (RCTs) for most of the risk factors, our model assumptions for the relative risks for risk factors were based on the best estimates available from long-term cohort studies.[10-18, 111] However, RCTs that estimated the effect of nonsteroidal anti-inflammatory drugs on adenoma recurrence[139] showed a smaller effect than what was observed from cohort and case-control studies. Thus, in the current study, we may have overestimated the benefits of risk factor modification.

Hormone replacement therapy (HRT) was not included as a risk factor in this analysis. Since the findings of the Women's Health Initiative (WHI) in 2002 that HRT use increases risk for cardiac events and breast cancer,[140] HRT use in the U.S. has declined sharply.[141] If HRT use is protective for CRC, then this decline will have a negative influence on CRC mortality trends in women. However, the potential effect will be modest: Only 25% of women age 40 years or older used HRT in 2001, and this rate declined to 15% in 2003. This 10% decline in women represents a <5% decline in the total population. Furthermore, with a possible relative risk of 0.8,[142] a protective effect of HRT would be modest. The U.S. Preventive Services Task Force recommends interpreting the evidence cautiously that suggests a protective effect of HRT. The WHI did show a reduction in CRC risk in women who used estrogen plus progestin and had an intact uterus, but patients with CRC in this intervention arm had more advanced disease and greater numbers of positive lymph nodes.[143] In women who underwent hysterectomy, no effect of only conjugated equine estrogen was found.[144] HRT, particularly estrogen only,[141] is used more commonly by women who have undergone a hysterectomy.[145]

In the model, we assume that risk factors only influence the incidence of adenomas. Risk factors also may influence the progression rate from adenoma to cancer. However, in this case, differences would be expected between the relative risks for cancers and adenomas. We observed only small differences between observed relative risks for adenomas and cancers.[10, 11, 14, 15, 17, 18] Thus, it is unlikely that risk factors have a large effect on adenoma progression rates. It is possible that a longer follow-up would demonstrate differences in relative risks for adenomas and cancers.

For the current analysis, we assumed that there was no correlation between the prevalence of individual risk factors. Although this assumption often is incorrect (e.g., there is a known correlation between lack of physical activity and obesity), in a similar multiplicative model of the effect of risk

factors on CRC, Cronin et al.[146] showed that the effect of a correlation on population-level risk is minimal. Their estimates for CRC incidence did not change significantly when they assumed an extreme correlation between risk factors instead of no correlation. In addition, we did not consider correlations between risk factor prevalence and the use of screening. Some studies of cancer screening have shown an association between low-risk patients and participation in screening.[147, 148] This implies that individuals who currently are not being screened for cancer have a greater risk of developing it; therefore, increased screening presumably will reach a higher risk population. This would increase the overall effect of screening.

The model assumes that all positive FOBTs and sigmoidoscopies are followed by colonoscopy and that the compliance with initial diagnostic and surveillance colonoscopies is 100%. However, a recent study has shown that only 63% of physicians and 76% of gastroenterologists and general surgeons recommend complete diagnostic evaluation of patients who have a positive FOBT result.[149] If compliance with diagnostic follow-up and surveillance were 80% rather than 100%, then the additional benefit of screening would be reduced to 14% rather than 17%.

Although treatment provided the least mortality reduction of the 3 interventions, increased use of chemotherapy still contributes substantially to reducing CRC mortality, especially in the short term. The hazard ratios associated with the different chemotherapy regimens were obtained from RCTs. The model assumes that the observed treatment effects persist over the long term, even though the actual follow-up for the newer CRC treatments still is quite short. Studies in Europe and Australia have shown improvements in survival attributable to improvements in surgery and specialization.[150-153] However, such improvements have not been the subject of RCTs. This makes these other factors difficult to quantify. Inclusion and extrapolation of these improvements through 2020 would lead to a greater decline in mortality than when accounting for chemotherapy alone.

Despite the uncertainties in parameters and assumptions, our model reproduced observed past trends in CRC incidence and mortality between 1980 and 2000 very well. Furthermore, with continued trends for risk factors, screening, and treatment, we project 55,500 new CRC deaths in 2006, which differs by <1% from the ACS projection of 55,170 CRC deaths.

The Healthy People Consortium and the ACS have recommended an objective to reduce CRC mortality by 34% in 2010[100] and by 50% in 2015,[101] respectively. Our current analysis shows that, even with optimistic trends, achieving these objectives is not feasible with current interventions. Newer prevention, screening, and treatment options, such as effective, low-risk chemoprevention,[154] virtual colonoscopy, fecal DNA screening, and new combination chemotherapies, will be necessary and likely will be developed. Further developments in the field of genomics and proteomics may increase the potential for targeted intervention strategies.

The projections for this study were developed as part of the NCI-sponsored Cancer Intervention and Surveillance Modeling Network Consortium to evaluate cancer trends and project the impact of future interventions. A website[155] is available for an interactive presentation of these analyses. The current analysis will be part of this website and will be refined and updated when new data become available.

In this study we demonstrated that an almost 50% reduction in CRC mortality by 2020 already is possible with currently available interventions. However, future trends in CRC mortality depend

greatly on the success of efforts to increase the use of current interventions. If we do not begin now to increase the uptake of current effective interventions, then CRC mortality reduction may be only 17%.

Chapter 4: At what costs will screening with CT colonography be competitive?

A cost-effectiveness approach

Abstract

The costs of computed tomographic colonography (CTC) are not yet established for screening use. In our study, we estimated the threshold costs for which CTC screening would be a cost-effective alternative to colonoscopy for colorectal cancer (CRC) screening in the general population. We used the MISCAN-Colon microsimulation model to estimate the costs and life-years gained of screening persons aged 50-80 years for 4 screening strategies: (i) optical colonoscopy; and CTC with referral to optical colonoscopy of (ii) any suspected polyp; (iii) a suspected polyp ≥6 mm and (iv) a suspected polyp ≥10 mm. For each of the 4 strategies, screen intervals of 5, 10, 15 and 20 years were considered. Subsequently, for each CTC strategy and interval, the threshold costs of CTC were calculated. We performed a sensitivity analysis to assess the effect of uncertain model parameters on the threshold costs. With equal costs ($662), optical colonoscopy dominated CTC screening. For CTC to gain similar life-years as colonoscopy screening every 10 years, it should be offered every 5 years with referral of polyps ≥6 mm. For this strategy to be as cost-effective as colonoscopy screening, the costs must not exceed $285 or 43% of colonoscopy costs (range in sensitivity analysis: 39-47%). With 25% higher adherence than colonoscopy, CTC threshold costs could be 71% of colonoscopy costs. Our estimate of 43% is considerably lower than previous estimates in literature, because previous studies only compared CTC screening to 10-yearly colonoscopy, where we compared to different intervals of colonoscopy screening.

4.1 Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States, with almost 149,000 new diagnosed cases and 50,000 deaths in 2008.[25] Screening can prevent many of these deaths, not only by detecting CRC in an early stage and thus improving prognosis but also by detecting and removing its nonmalignant precursor lesion, the adenoma, and thus preventing CRC incidence. Randomized controlled trials have shown that biennial and annual screening with the fecal occult blood test (FOBT) can reduce CRC mortality by 15-33%.[28, 29, 31, 156] FOBT is a cheap and non-invasive test, but it still leaves many cancers undetected[28, 81, 82, 157] and there is therefore room for improvement. Endoscopy is highly sensitive for CRC and adenomas.[92, 117, 118, 158, 159] Case-control studies have suggested that endoscopic screening is associated with a substantial reduction in CRC mortality.[44, 46, 160, 161] Nonetheless, its efficacy in screening is yet to be quantified by large randomized controlled trials, several of which are currently underway.[56, 162-164] Limitations of endoscopy screening include cost, risk of severe complications and hesitancy of patients to undergo these tests. Furthermore, there are currently insufficient well-trained gastroenterologists to meet projected screening endoscopy needs.[165]

Computed tomographic colonography (CTC) is a promising technique for CRC screening, combining high sensitivity for larger polyps and cancer[50, 166] with a less invasive procedure.[167, 168] With CTC 2- and 3D images of the colon and rectum are constructed to investigate the presence of lesions. A serious potential drawback is that conventional (optical) colonoscopy is required to further evaluate and remove the abnormalities detected through CTC. Several studies have shown that CTC is currently not a cost-effective option for average-risk CRC screening if all suspected polyps are followed up by optical colonoscopy.[169-171] CTC could be cost-effective if diagnostic follow-up is only recommended for patients with suspected polyps of 6 mm or larger.[172, 173] However, CTC screening for CRC remains under development and therefore its costs have not yet been established. As a consequence, different cost-effectiveness estimates are often based on fairly different cost assumptions.

In our study, we used the MISCAN-Colon microsimulation model to estimate the life-years gained and costs of CTC screening for various screen intervals and polyp size thresholds for diagnostic follow-up for different levels of unit CTC costs and compared the cost-effectiveness to colonoscopy screening. Furthermore, we determined the threshold CTC unit costs for which CTC screening would be cost-effective compared to colonoscopy screening. Finally, we placed the results in the context of other studies in a literature overview of CTC cost-effectiveness analyses.

4.2 Material and methods

MISCAN-Colon microsimulation model

The Department of Public Health at Erasmus MC, the Netherlands, developed the MISCAN-Colon microsimulation model in collaboration with the U.S. National Cancer Institute to assess the effect of different interventions on CRC. The model and the data sources that inform the quantification of the model can be found in the model appendix, in previous publications,[75-77] and in a standardized model profile.[78] A graphical representation of the natural history in the model is given in Figure 1.8. In brief, the MISCAN-Colon model simulates the relevant biographies of a large population of individuals from

birth to death, first without screening and subsequently with the changes that would occur under the implementation of a screening program. CRC arises in this population according to the adenoma-carcinoma sequence.[22, 23] More than 1 adenoma can occur in an individual and each can independently develop into CRC. Adenomas progress in size from small (1-5 mm) to medium (6-9 mm) to large (≥10 mm). Most adenomas will never grow into cancer in a lifetime (non-progressive adenomas). These adenomas either stay 6-9 mm in size or continue to grow to 10 mm or larger. Some adenomas (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage, there is a probability of the cancer being diagnosed because of symptoms versus alternatively progressing without symptoms into the next stage. However, a person may die of other causes at any time during the process before diagnosis. The survival after clinical diagnosis depends on the stage in which the cancer was detected. Once a life history without screening is established, screening is simulated and whether it interrupts the development of CRC. With CTC screening, polyps of different sizes are detected. After a person is detected with polyps above the follow-up cut-off size, he is referred for follow-up optical colonoscopy for removal of adenomas and diagnosis of cancers. In this way, CRC incidence or CRC death can be prevented. The life years gained by screening are calculated by comparing the model predicted life-years lived in the population with and without screening.

The validity of the model is based on observational data before the introduction of screening, such as clinical incidence and mortality from CRC[135] and the size and multiplicity distribution of adenomas in autopsy studies.[174-183] The external validity has further been tested on the results of large (randomized) screening and surveillance studies, such as the CoCap sigmoidoscopy study,[75] the Minnesota Colon Cancer Control Study[75] and the National Polyp Study.[184] Finally, the model was able to explain observed incidence and mortality trends in the U.S. when accounting for risk factor trends, screening practice and chemotherapy treatment.[185]

Screening characteristics

The assumptions for sensitivity and specificity of CTC (Table 4.1) were based on the meta-analysis of Mulhall et al.[50] Mulhall et al. conducted a meta-analysis for per-patient sensitivity. For the MISCAN-Colon model, we needed per-adenoma sensitivity, so we repeated the meta-analysis for per-adenoma sensitivity based on the original studies included by Mulhall et al. Non-adenomatous polyps were not explicitly modeled. However, we did take into account the costs and complications incurred by the detection and removal of non-adenomatous polyps with CTC and colonoscopy. We adjusted the specificity estimates for not having polyps in the Mulhall et al. study to an estimate for not having adenomas, by subtracting the proportion of patients with non-adenomatous polyps only from the specificities reported. This higher lack of specificity resulted in a larger number of patients being referred for colonoscopy and receiving polypectomy and pathology. This lack of specificity also ensured the possibility of detection and removal of coexisting smaller adenomas or even missed larger polyps, which were otherwise not referred for colonoscopy. In a screening population, 33.3% (CI 30.6-36.0%) of individuals only have non-adenomatous polyps, 8.8% (CI 7.3-10.6%) only have non-adenomatous polyps of 6 mm or larger and 2.0% (CI 1.3-3.0%) of 10 mm or larger.[186]

Table 4.1: Screening test characteristics for CTC (confidence interval) and optical colonoscopy, used as inputs for the MISCAN-Colon model

Parameter	CTC	Optical colonoscopy
Sensitivity (%)		
Small adenomas (1-5 mm)	29 (22-37)	75
Medium adenomas (6-9 mm)	66 (59-72)	85
Large adenomas (≥10 mm)	87 (82-93)	95
Cancers	87 (82-93)	95
Specificity (%)	Cut-off 0 mm: 53 (50-55) Cut-off 6 mm: 84 (83-86) Cut-off 10 mm: 95 (94-96)	90
Reach	100% reach cecum	95% reach cecum, reach of remaining 5% is distributed evenly over colorectum
Nonfatal complication rate	n.a.	2.4 per 1000
Fatal complication rate	n.a.	0.1 per 1000

n.a. = not applicable.

The sensitivity and specificity of optical colonoscopy were based on back-to-back colonoscopy studies (Table 4.1).[117, 118, 159] The lack of specificity for optical colonoscopies reflected the fact that in 10% of persons without adenomas, additional costs were incurred because of removal and pathology of non-adenomatous polyps. The rate of serious nonfatal complications was assumed to be 2.4 per 1000 colonoscopies.[58, 187-189] The rate of fatal events was assumed 0.1 per 1000 colonoscopies.[190]

Cost inputs

Colonoscopy costs were based on 2007 Medicare average payments (including beneficiary co-pays).[42] CTC screening is currently not reimbursed by Medicare, and hence, no average payments are available. We therefore considered different cost levels for CTC: same as, half of and one-third of colonoscopy costs. Finally, we varied the unit costs of CTC to determine the threshold costs for which it would be a cost-effective alternative to colonoscopy screening. Because these threshold costs are derived relative to the cost-effectiveness of colonoscopy under Medicare average payments, they include the same components as the colonoscopy costs.

The costs of complications requiring inpatient hospitalization were based on the relevant Diagnostic Related Group (DRG) codes.[42] The phase-specific cost of CRC treatment was derived from comparison of costs for CRC cases relative to those of matched controls in the SEER-Medicare files.[191] Treatment cost data were reported in 2004 dollars and subsequently 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 4.2.

Table 4.2: Unit costs in 2007$ for screening and CRC treatment, used as inputs for the MISCAN-Colon model

Screening Costs		CRC Treatment Costs				
Procedure	Cost	Stage	Initial*	Continuous*	Terminal care, death CRC*	Terminal care, death other cause*
Colonoscopy	$662	I	$28,668	$2,395	$51,935	$12,703
Colonoscopy with polypectomy	$846	II	$39,700	$2,237	$51,712	$11,035
CTC	Varied	III	$48,951	$3,249	$54,776	$14,708
Treatment of complications	$5,182	IV	$64,801	$10,419	$73,522	$39,679

* Costs for 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 following 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 last year of life phases of care. The terminal care phase of CRC patients was further subdivided into terminal care before CRC death and terminal care before death of other causes. Cause of death was identified by use of death certificate information in the SEER database. 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.

Screening strategies

We simulated 4 colonoscopy and 12 CTC screening strategies. In all strategies, screening began at age 50 and was discontinued after age 80. Screen intervals of 20, 15, 10 and 5 years were considered. This corresponded with 2, 3, 4 and 7 screens offered in a lifetime, respectively. With CTC screening, we simulated 3 different follow-up strategies:

1. Intensive referral: any suspected polyp detected, irrespective of size,
2. Intermediate referral: suspected polyps of 6 mm or larger detected, and
3. Minimal referral: suspected polyps of 10 mm or larger detected.

Persons without referral for diagnostic colonoscopy or without adenomas detected at (diagnostic) colonoscopy continued in the CTC screening program. If an adenoma was detected and thus removed at colonoscopy, surveillance was conducted according to the guidelines of the U.S. Multi-Society Task Force on Colorectal Cancer.[192] Adherence with screening, diagnostic follow-up and surveillance were assumed to be 100%.

Analysis

For each of the 16 screening strategies, we calculated life-years gained, number of screen tests and costs. Future costs and life years were discounted at an annual rate of 3%. We plotted the costs and life-years gained from the colonoscopy strategies on a graph and connected the strategies by a line, representing the colonoscopy cost-effectiveness frontier (Figures 4.1 and 4.2). For the CTC strategies to be a cost-effective alternative for colonoscopy screening, the strategies needed to be on or to the left of this line. We plotted the costs and life-years gained with the different CTC screening strategies in the same plot for different CTC cost levels: same as colonoscopy costs, half of colonoscopy costs and one third of colonoscopy costs (Figures 4.1a-4.1c respectively). Finally, we determined the threshold costs for which each of the CTC screening strategies was on the colonoscopy cost-effectiveness frontier (Figure 4.2). There were 3 possible situations to consider: (i) the CTC strategy was less effective than the least effective colonoscopy strategy, (ii) the CTC strategy was more effective than the most effective colonoscopy strategy and (iii) the effectiveness of the CTC test strategy was intermediate to the least effective and most effective strategies on the colonoscopy cost-effectiveness frontier. In the 1st case, the threshold costs of CTC were calculated such that the average costs per life-year gained for the CTC strategy were equal to those of the least effective colonoscopy strategy. In the 2nd case, the threshold test costs were calculated such that the incremental costs per life-year gained for the CTC strategy compared to the most effective colonoscopy strategy were equal to $50,000 per life-year gained. In the 3rd case, we identified the colonoscopy strategy with lowest life-years gained that would still have more life-years gained than the CTC strategy. Subsequently, the threshold costs were calculated such that the incremental costs per life-year gained of the CTC strategy were equal to those of that selected strategy.

We looked at the effect of differential adherence between colonoscopy and CTC on the threshold costs for CTC. We compared costs and effects of colonoscopy screening with current adherence[108] (75% of patients had colonoscopy at least once during their lifetime, 45% according to recommendation) to CTC screening with adherence rates comparable to that of mammography screening[193] (90% had CTC at least once during their lifetime, 70% according to recommendation). Finally, we performed a sensitivity analysis for uncertain model parameters to assess their effect on the threshold costs. CTC sensitivity and specificity estimates were set at the lower and higher range of their confidence intervals (Table 4.1). Natural history parameters varied were the average duration of the adenoma-carcinoma sequences (base value: 20 years, values considered: 10, 30 and 40 years) and the variance of the duration, assessed as the percent of cancers that develop within 5 years (base value: 22%, values considered: 1, 5, 10 and 25%). All of the alternative natural history models were calibrated to age-specific SEER CRC incidence.[135]

4.3 Results

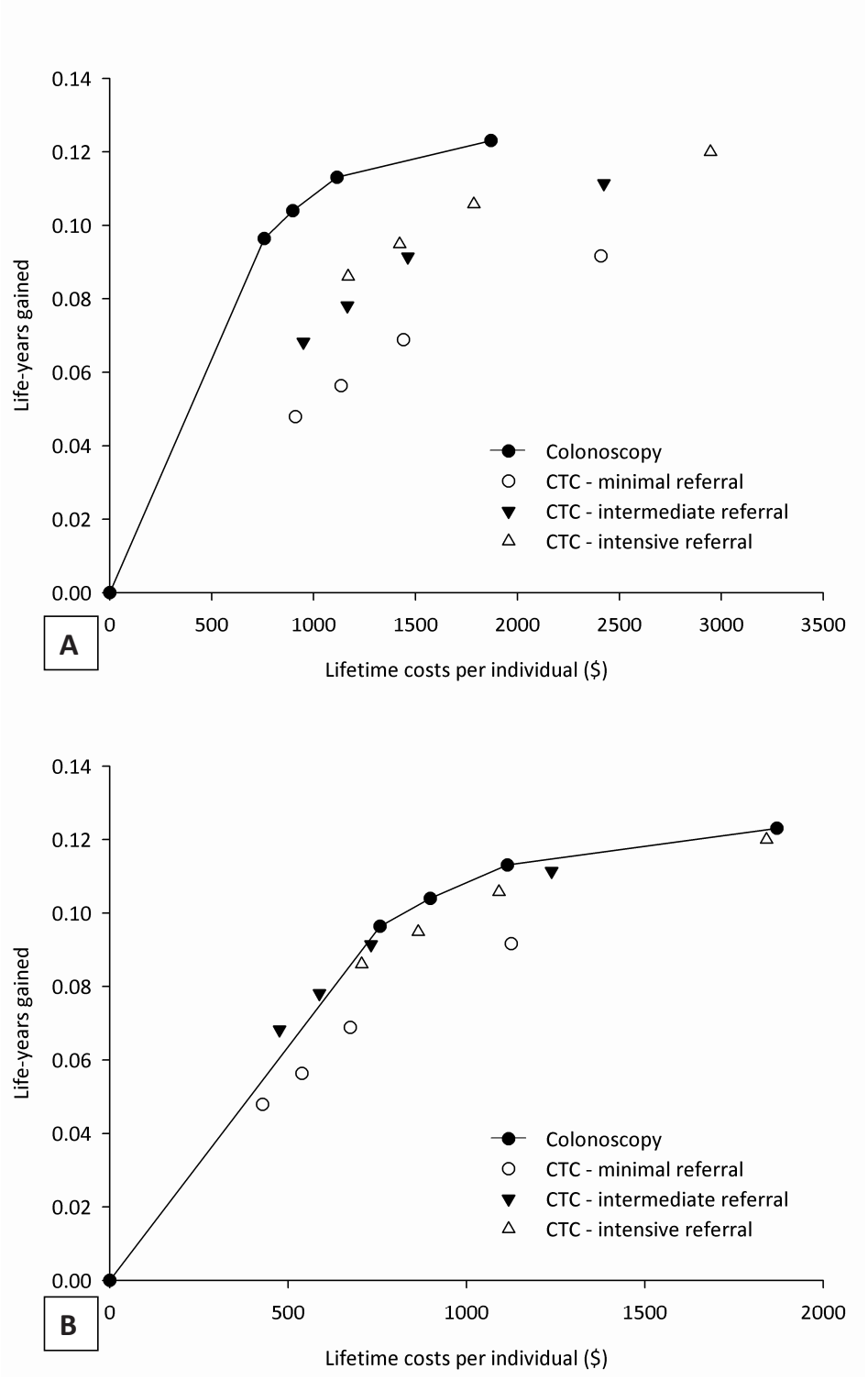
The colonoscopy strategies varied in life-years gained from 0.096 per individual entering the program with a screening interval of 20 years to 0.123 with a 5-year interval (Table 4.3, 3% discounted results). The costs for colonoscopies increased from $1,900 for 2 screening colonoscopies to $3,364 for 7 colonoscopies. This increase is smaller than one may have expected, because of surveillance colonoscopies. The savings increased from $1,142 to $1,494. The current screening recommendation of colonoscopy screening every 10 years saved 0.113 life-years. CTC screening resulted in comparable life-years gained when performed every 5 years with intermediate or intensive referral. The life-years gained with CTC screening varied from 0.048 to 0.120. CTC screening induced lower colonoscopy costs than with colonoscopy screening but required additional CTC screen tests varying from 1.40 to 3.88 per individual (undiscounted results are presented in the Appendix Table to this chapter).

With CTC unit costs equal to colonoscopy costs ($662), CTC screening was dominated by colonoscopy screening (Figure 4.1A). The CTC screening strategies saved fewer life-years than colonoscopy screening for the same costs or required more costs to save the same number of life-years. Of the CTC screening strategies, CTC with intensive referral was least dominated. With CTC costs of $331 (half of colonoscopy costs), intermediate referral was the most cost-effective CTC screening strategy. However, only the intermediate referral strategy offered every 15 or 20 years was a cost-effective alternative for colonoscopy screening (Figure 4.1B). With CTC costs of $221 (one-third of colonoscopy costs), most CTC screening strategies were a cost-effective alternative to colonoscopy screening (Figure 4.1C). Intermediate referral remained the preferred strategy.

Table 4.3: Lifetime CTC tests, colonoscopy costs, treatment savings and life-years gained per individual for different follow-up strategies of CTC compared to colonoscopy screening (3% discounted)

Screening strategy*		#CTC tests	Colonoscopy costs ($)[†]	Treatment savings ($)[‡]	Life-years gained[‡]
Colonoscopy					
Interval:	20 years	0	1,900	1,142	0.096
	15 years	0	2,137	1,238	0.104
	10 years	0	2,467	1,352	0.113
	5 years	0	3,364	1,494	0.123
CTC- minimal referral					
Interval:	20 years	1.46	438	492	0.048
	15 years	1.80	512	570	0.056
	10 years	2.32	590	682	0.069
	5 years	3.88	735	892	0.092
CTC- intermediate referral					
Interval:	20 years	1.43	769	767	0.068
	15 years	1.75	885	875	0.078
	10 years	2.21	1,019	1,017	0.091
	5 years	3.58	1,289	1,236	0.111
CTC- intensive referral					
Interval:	20 years	1.40	1,242	999	0.086
	15 years	1.68	1,410	1,103	0.095
	10 years	2.10	1,625	1,230	0.106
	5 years	3.34	2,141	1,406	0.120

Minimal referral = referral of patients with findings at CTC of 10 mm or larger.
Intermediate referral = referral of patients with findings at CTC of 6 mm or larger.
Intensive referral = referral of patients with any findings at CTC.
* An interval of 20 years corresponds with 2 screens in a lifetime, 15 years with 3 screens, 10 years with 4 screens and 5 years with 7 screens.
[†] Including costs for screening, diagnostic and surveillance colonoscopies and treatment of complications due to colonoscopy. CTC screening costs are not included.
[‡] Compared to situation without screening.


0.14
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Life-years gained
0
500
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2000
2500
3000
3500
Lifetime costs per individual ($)
Colonoscopy
CTC - minimal referral
CTC - intermediate referral
CTC - intensive referral
A
0.14
0.12
0.10
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Life-years gained
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Lifetime costs per individual ($)
Colonoscopy
CTC - minimal referral
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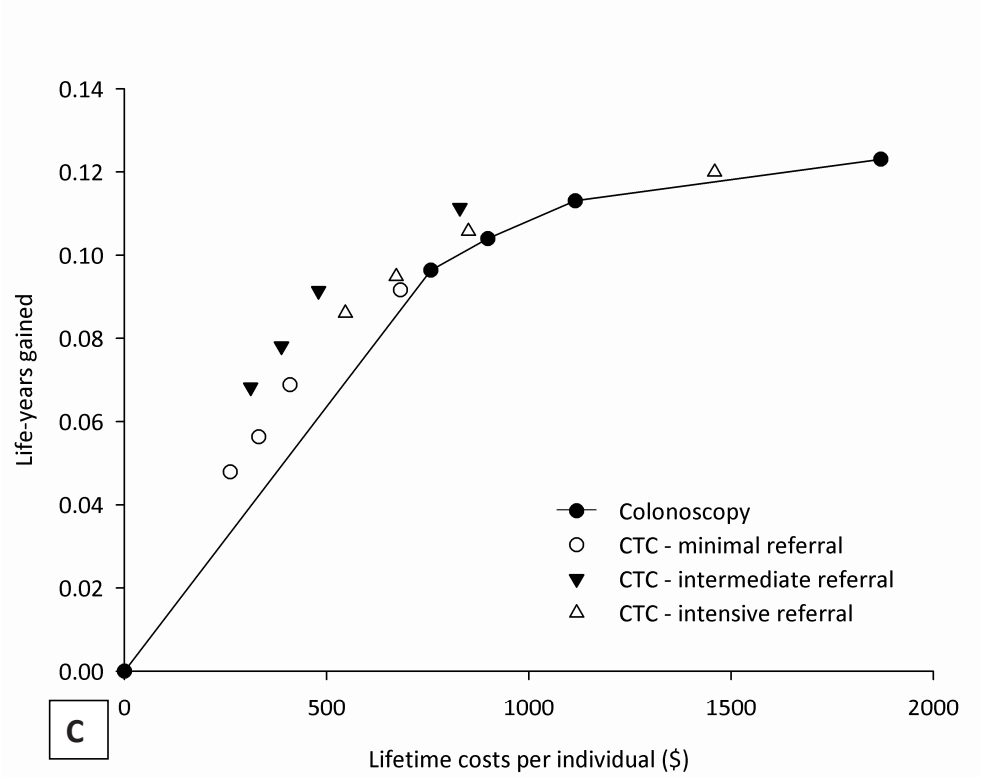

Figure 4.1: The net costs required over a lifetime and the life-years gained (3% discounted and compared to a situation without screening) for screening a cohort of 50-year olds according to different colonoscopy and CTC screening strategies varying with respect to screening interval and referral threshold. Lifetime costs include costs for screening, diagnostic and surveillance colonoscopy minus the savings from treatment compared to a situation without screening. The dark circles represent the colonoscopy strategies; the open circles CTC strategies with minimal referral, the reverse triangles CTC with intermediate referral and the open triangles CTC strategies with intensive referral. From left to right the symbols per strategy represent intervals of 20, 15, 10 and 5 years. The solid line represents the cost-effectiveness of colonoscopy screening strategies, corresponding with Table 4.3. CTC costs are equal to colonoscopy costs in Figure 4.1A, half of colonoscopy costs in Figure 4.1B and one-third of colonoscopy costs in Figure 4.1C

Threshold analysis

Figure 4.2 shows the threshold costs for the non-dominated CTC screening strategies to have equal incremental costs per life-year gained as colonoscopy screening. CTC screening every 20 years with intermediate referral had the highest threshold costs of $373. However, the life-years gained with this strategy are much lower than with the current recommendation of colonoscopy every 10 years. With increasing screening intensity, the threshold costs of CTC decreased. A strategy that is comparable to the current recommendation with respect to life-years gained is CTC screening every

5 years with a referral threshold of 6 mm. For this strategy to have the same incremental costs per life-year gained as 10-yearly colonoscopy, the unit costs of CTC needed to be $285 or lower. With 25% higher adherence for CTC than for colonoscopy, threshold costs of 5-yearly CTC with intermediate referral increased to $470.

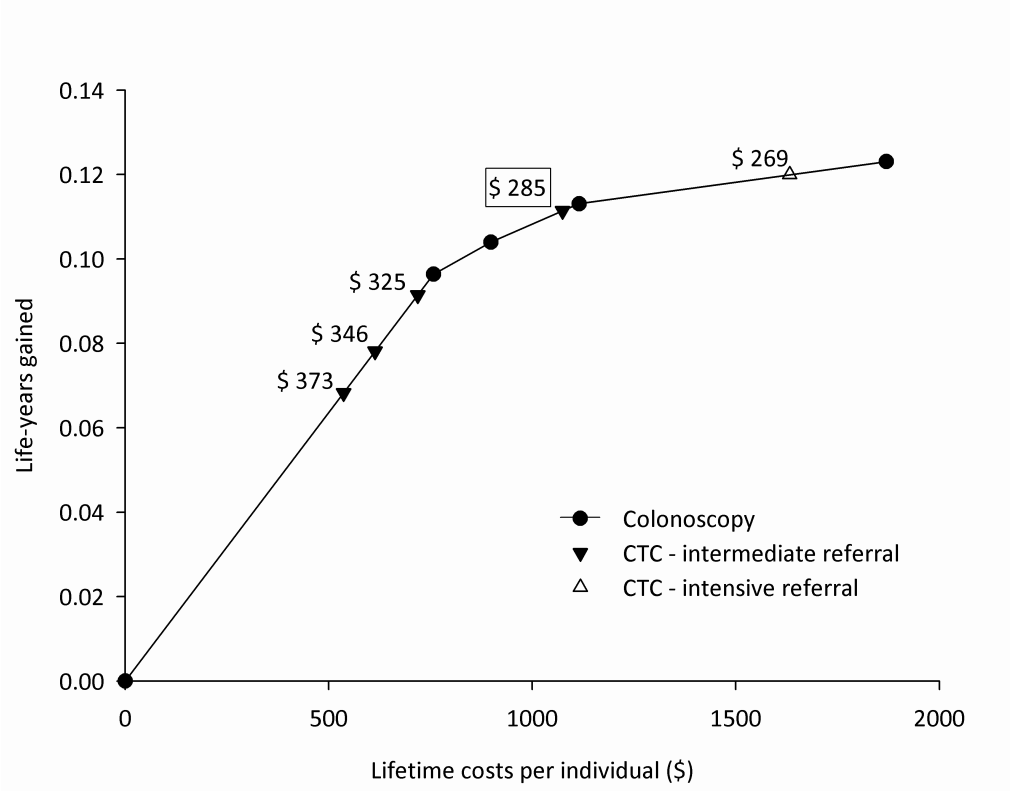

Figure 4.2: The threshold costs of non-dominated CTC strategies for which the strategies are a cost-effective alternative to colonoscopy screening. The reverse triangles represent CTC screening with intermediate referral. From left to right the triangles represent screening intervals of 20, 15, 10 and 5 years. The open triangle represents CTC screening every 5 years with intensive referral. The costs next to the symbols per strategy indicate the threshold unit costs for CTC to be cost-effective compared to colonoscopy screening. The boxed cost is the threshold costs for 5-yearly CTC with intermediate referral, the strategy with similar life-years gained as 10-yearly colonoscopy.

Sensitivity analysis

The worst- and best-case scenarios for CTC test characteristics yielded a similar ordering of strategies as the base-case analysis. The threshold costs for CTC every 5 years with a referral threshold of 6 mm were $313 for the best-case scenario and $264 for the worst-case analysis. Varying the mean duration of the adenoma-carcinoma sequence from 20 to 10, 30 or 40 years did not change the threshold costs much: the threshold costs for CTC every 5 years with intermediate referral were

$284, $282 and $277, respectively. Changing the variation in the duration of the adenoma-carcinoma sequence had somewhat more influence. CTC screening every 5 years with intermediate referral remained the strategy with similar life-years gained as colonoscopy every 10 years and the threshold costs for this strategy were $260 if 1% of cancers progress within 5 years (base-case 22%), $265 if 5%, $271 if 10% and $284 if 25% of cancers progress within 5 years.

4.4 Discussion

In our study, we found that at costs of $285 per test CTC screening would be a cost-effective alternative to provide similar life-years gained as the currently recommended strategy of colonoscopy screening every 10 years, provided that CTC screening would be offered every 5 years with follow-up restricted to findings of 6 mm or larger. Our results were very robust for changes in CTC test characteristics and natural history assumptions. CTC with intermediate referral remained the most-cost-effective CTC screening strategy in the majority of sensitivity analyses. The threshold costs for this strategy varied from $260-$313, 53-61% lower than that of optical colonoscopy. Assuming differential adherence for CTC and colonoscopy had more effect on threshold costs. In the extreme scenario in which CTC would be able to increase screening adherence with 25% compared to colonoscopy, the threshold costs for CTC still needed to be 30% lower than colonoscopy costs.

Our results support the expectations of clinicians that follow-up of small findings at CTC is not efficient.[194] Small adenomas are common and most will never develop into CRC. Furthermore, small findings at CTC are often non-adenomatous polyps or even artifacts, negatively influencing the specificity of CTC. Of course, when ignoring small findings and because of the lower sensitivity of CTC for small adenomas, the preclinical screen-detectable period is shorter than with colonoscopy screening. We showed that with a mean dwelling time of 9.1 years for adenomas of 1-5 mm and of 7.3 years for an adenoma of 6 mm to preclinical cancer (which is less than the screening interval of 10 years), CTC should be offered at an interval of 5 years to be as effective as colonoscopy every 10 years. Some radiologists and gastroenterologists suggest that follow-up could be restricted to polyps of 10 mm or larger.[194] They argue that dysplasia and malignancy occur too rarely in smaller adenomas to warrant diagnostic follow-up and polypectomy. The rate of malignant transformation may indeed be up to 10 times higher in large polyps than in small polyps.[195, 196] However, small and medium adenomas are almost 10 times more prevalent than large adenomas,[174, 183] making the CRC incidence from small and medium adenomas potentially as high as that from large adenomas.[197, 198] This becomes clear from the results of our study: In none of the analyses was CTC screening cost-effective with only follow-up of lesions of 10 mm or more.

The strength of CTC, to be able to distinguish between low-risk and high-risk individuals for CRC, may also turn out to be its weakness. Despite the fact that small findings are ignored with CTC, they are present and will frequently be seen. Then questions of ethics arise: is it ethical not to register and/or to inform patients about this finding? Informing about these findings without taking action on them will induce anxiety in otherwise healthy individuals. The shorter screening interval in the strategy with a higher referral threshold takes away some of the concerns. The probability that adenomas less than 6 mm will grow into cancer within 5 years is small. The shorter interval further offers the possibility to detect previously missed lesions. Also, it should be noted that setting thresholds for further action is inherent to screening. Ignoring small findings with CTC is, in terms of risk

management, not that different from the cut-off levels used for a positive test result with for example PSA testing or immunochemical FOBT. If, however, it would be decided that ignoring of small findings at CTC is unacceptable, this will further decrease the threshold costs to 39-41% of colonoscopy costs, depending on the interval chosen.

In our analysis, we assumed that restriction of follow-up did not impair CTC sensitivity. However, radiologists may over- or underestimate the real size of an adenoma.[199] When restricting follow-up to adenomas of 6 or 10 mm or larger, some lesions will be misclassified as smaller and wrongfully not be followed up. Some small lesions will also be overestimated in size and will be followed up, but the benefit of their removal is smaller than of removal of larger adenomas. Errors in size estimation are therefore likely to make intensive referral more favorable compared to intermediate or minimal referral.

CTC screening is a non-invasive alternative to colonoscopy screening and is not associated with the major complications of colonoscopy such as perforations, serosal burns and bleeds.[58, 187-189] A recent study, comparing CTC and colonoscopy for CRC screening,[200] reported 7 serious adverse events in 3,163 people undergoing colonoscopy, and no complications in 3,120 people undergoing CTC. However, CTC is associated with exposure to radiation, which we did not consider in our analysis. Brenner and Georgsson[201] estimated that the excess cancer risk from a pair of CTC scans using typical current scanner techniques is about 0.14% for a 50-year old and half that for a 70-year old. This estimate is controversial, because it was based on simulation calibrated to atomic bomb survivors. Multiple CTC screens will increase the radiation dose proportionally and most likely also the radiation risks. We found that CTC is only compatible to colonoscopy screening if offered 7 times (every 5 years between ages 50 and 80), potentially leading to an excess cancer risk of ~0.47%. This will lead to life-years lost due to CTC, which are not negligible compared to the life-years gained. We did not take these excess cancer cases into account, because there is good evidence that radiation dose with CTC can be reduced by at least a factor of 5 (and perhaps as much as 10), while still maintaining sensitivity and specificity for polyps larger than 5 mm.[201] With these dose reductions, excess risk of cancer from CTC becomes negligible.

Several other studies have been published on the cost-effectiveness of CTC screening in the general population (Table 4.4). In all these studies, the threshold costs for CTC screening were higher than the 43% of colonoscopy costs found in our study. An important reason for this is that we compared CTC screening to different intervals of colonoscopy screening, whereas the other studies compared CTC only to 10-yearly colonoscopy. Sonnenberg et al. estimated that 10-yearly intensive CTC should cost 46% of colonoscopy costs to have the same costs per life-year gained.[171] The same comparison in our study yields similar threshold costs (47%, footnote Table 4.4). The estimated threshold costs from Ladabaum et al. were slightly higher (60%), but they assumed better CTC test sensitivity.[170] Vijan et al. compared CTC every 5 years (referral of all lesions) to 10-yearly colonoscopy.[202] They found threshold costs of 75% of colonoscopy costs. The same comparison in our study yields costs of 33% (footnote Table 4.4). This is explained by better test characteristics (especially for specificity) based on 3D CTC in Vijan et al.'s assumptions. Using the performance characteristics of 2D CTC (which had slightly lower sensitivity than in this analysis, but still better specificity), Vijan et al. found very low CTC threshold costs, which corresponds with our finding of 33%. Finally, Pickhardt et al. compared 10-yearly CTC screening with a referral threshold of 6 mm to 10-yearly colonoscopy screening.[172] He found that with CTC costs at 70% of colonoscopy costs, CTC screening with referral

of lesions 6 mm or larger was cost-effective compared to colonoscopy. This is somewhat higher than the estimate from the same comparison in our study (62%). Our study adds that to compete with colonoscopy cost-effectiveness, one must consider different intervals of colonoscopy screening. This is necessary to ascertain that CTC screening is not dominated by colonoscopy screening. In Figure 4.2, this is represented by the (incremental cost-effectiveness) lines connecting the colonoscopy strategies. It is harder for 5-yearly intermediate CTC screening to achieve a level on the cost-effectiveness frontier line connecting 15-yearly colonoscopy and 10-yearly colonoscopy than to get on the line connecting no screening (the origin) to 10-yearly colonoscopy.

Table 4.4: Literature overview of studies estimating the cost-effectiveness of CTC screening in the average-risk population

Study*	Comparator strategy	Sensitivity of CTC for adenomas	Specificity CTC	Threshold costs as % of cspy costs
Lansdorp-Vogelaar	Several cspy strategies	Small: 29% Medium: 66% Large: 87%	Referral 0 mm: 53% Referral 6 mm: 84% Referral 10 mm: 95%	43%, for 5-yearly CTC, referral 6 mm
Sonnenberg et al., 1999	10-yearly cspy	80%	95%	46% for 10-yearly CTC, referral 0 mm*
Ladabaum et al., 2004	10-yearly cspy	Small: 87% Medium: 87% Large: 94%	85%	60% for 10-yearly CTC, referral 0 mm*
Vijan et al., 2007	10-yearly cspy	Small: 46% Medium: 83% Large: 91%	91%	75% for 5-yearly CTC, referral 0 mm†
Pickhardt et al., 2007	10-yearly cspy	Small: 48% Medium: 70% Large: 85%	86%	>70% for 10-yearly CTC, referral 6 mm‡

Cspy = colonoscopy.
* Comparison of the same strategies in our model yielded threshold costs of 47%.
† Comparison of the same strategies in our model yielded threshold costs of 33%.
‡ Comparison of the same strategies in our model yielded threshold costs of 62%.

CTC remains under development. The development of computer-assisted reading of the images and detection of lesions has potential for decreasing radiologists reading time and therewith reducing costs.[203] Furthermore, the potential introduction of CTC without cathartic preparation will further reduce the inconvenience of patients, and therefore probably increase adherence with CTC.[204, 205] These developments will have to be monitored for updating the comparative evaluation between

CTC and other screening modalities. Our analysis shows that CTC can be a cost-effective alternative for CRC screening in the general population if offered every 5 years, diagnostic follow-up is restricted to those with polyps of 6 mm or larger and CTC costs less than 43% of colonoscopy costs. In view of the aforementioned developments, this level of CTC costs may be possible.

Appendix Table, chapter 4: Lifetime CTC tests, colonoscopy costs, treatment savings and life-years gained per individual for different follow-up strategies of CTC compared to colonoscopy screening (undiscounted)

Screening strategy*		#CTC tests	Colonoscopy costs ($)[†]	Treatment savings ($)[‡]	Life-years gained[‡]
Colonoscopy					
Interval:	20 years	0	2,608	2,459	0.231
	15 years	0	3,046	2,674	0.249
	10 years	0	3,541	2,903	0.271
	5 years	0	4,844	3,175	0.294
CTC- minimal referral					
Interval:	20 years	1.83	740	1,117	0.116
	15 years	2.43	886	1,303	0.137
	10 years	3.18	1,011	1,538	0.167
	5 years	5.44	1,237	1,962	0.219
CTC- intermediate referral					
Interval:	20 years	1.78	1,251	1,706	0.165
	15 years	2.32	1,472	1,951	0.189
	10 years	2.99	1,680	2,238	0.220
	5 years	4.95	2,083	2,668	0.266
CTC- intensive referral					
Interval:	20 years	1.72	1,899	2,174	0.206
	15 years	2.21	2,208	2,409	0.228
	10 years	2.81	2,535	2,664	0.253
	5 years	4.57	3,285	3,006	0.286

Minimal referral = referral of patients with findings at CTC of 10 mm or larger.
Intermediate referral = referral of patients with findings at CTC of 6 mm or larger.
Intensive referral = referral of patients with any findings at CTC.
* An interval of 20 years corresponds with 2 screens in a lifetime, 15 years with 3 screens, 10 years with 4 screens and 5 years with 7 screens.
[†] Including costs for screening, diagnostic and surveillance colonoscopies and treatment of complications due to colonoscopy. CTC screening costs are not included.
[‡] Compared to situation without screening.

Chapter 5: Rising chemotherapy costs make colorectal cancer screening cost-saving

Abstract

Background: Although colorectal cancer (CRC) screening is cost-effective, it requires a considerable net investment. If screening would be cost-saving, governments and insurance companies might be more inclined to invest in CRC screening programs. We analyzed if CRC screening could become cost-saving with the widespread use of new chemotherapies.

Methods: We used the MISCAN-Colon microsimulation model to estimate how widespread use of new chemotherapies affected the treatment savings of CRC screening in the general population. With these chemotherapies, we assumed better survival and higher treatment costs for advanced CRC stages. Screening strategies considered were annual fecal occult blood testing (FOBT), annual immunochemical FOBT, 5-yearly sigmoidoscopy, 10-yearly colonoscopy and the combination of 5-yearly sigmoidoscopy and annual FOBT.

Results: Compared to no screening, the treatment savings from preventing advanced CRC and CRC deaths by screening more than doubled with the widespread use of new chemotherapies. The savings with FOBT (life-time savings $1,387 per individual in the population), immunochemical FOBT ($1,744), sigmoidoscopy ($1,695) and the combination of sigmoidoscopy with FOBT ($1,919) became larger than the life-time screening costs ($859, $1,565, $1,691 and $1,882 per individual respectively). Colonoscopy did not become cost-saving, but the total net costs of this strategy decreased from $1,422 to $413 per individual in the population.

Conclusions: By the increase in chemotherapy costs of advanced CRC, most CRC screening strategies have become cost-saving. As a consequence, screening is not only desirable for governments and insurance companies to reduce CRC incidence and mortality, but also to contain treatment costs of CRC.

5.1 Introduction

Almost 149,000 thousand persons in the U.S. are newly diagnosed with colorectal cancer (CRC) each year.[25] About one-third of these patients die of the disease, making CRC the second leading cause of cancer death. CRC deaths can be prevented. Recent trials have shown that breakthroughs in chemotherapy can lengthen median survival of patients diagnosed with metastatic CRC from 14 months with 5-fluorouracil and leucovorin (5-FU) to 21 months with anti-VEGF and combination chemotherapy.[66] However, these achievements came with a considerable price tag. The additional 7 months of survival have been accompanied by a 340-fold increase in drug costs.[206] The total costs for the management of CRC are currently estimated at $3.18 billion and expected to increase to $5.19 billion by 2020.[207]

Screening is the other cornerstone for reducing the number of life-years lost due to CRC. Its long preclinical duration and the favorable survival at early detection, make CRC suited for screening. Randomized controlled trials have shown that biennial and annual screening with Hemoccult II can reduce CRC mortality with 15% to 33%.[28, 29, 31, 85, 156] Although the extent of the efficacy of screening by endoscopy for the prevention of CRC has yet to be demonstrated by prospective randomized controlled trials,[56, 160, 162-164] several case-control studies suggest that endoscopic screening is associated with a 50-90% reduction in CRC incidence and mortality.[44, 46, 161] CRC screening is not only an effective tool for reducing CRC mortality, it is also estimated to reach this goal at very acceptable costs.[72] The estimated average costs per life-year gained with Hemoccult II screening varied in different publications between $5,691 and $17,805. This is well below the frequently used cost-effectiveness threshold for medical interventions of $50,000 per life-year gained. This also holds for colonoscopy screening, where estimates vary between $8,840 and $22,012 per life-year gained and for sigmoidoscopy screening with estimates between $12,477 and $39,539.

Although these cost-effectiveness ratios are very favorable, CRC screening still requires a considerable net investment. This has made insurance companies and governments hesitant to implement CRC screening programs. However, these cost-effectiveness studies do not yet include the spectacular rise in CRC treatment costs. Interestingly, where treatment costs for advanced CRC (and thus the savings when these are prevented) have substantially increased over the past decade,[206, 208] costs of screening have remained stable.[42, 209] No studies have explicitly looked at the effect of the rising treatment costs on the costs and savings of CRC screening. This is however of major importance in the decision process for introduction of population CRC screening programs, a process which is currently ongoing in many countries worldwide. If screening would become cost-saving, governments and insurance companies might be more inclined to invest in CRC screening programs because these investments will be earned back in the near-future. In this analysis, we used the MISCAN-Colon microsimulation model to test the hypothesis that CRC screening would become cost-saving with the widespread use of new chemotherapeutic agents.

5.2 Methods

MISCAN-Colon microsimulation model

The MISCAN microsimulation model was developed at the Department of Public Health, of Erasmus MC, the Netherlands, and has been used to evaluate breast, cervical, colon, and prostate cancer screening programs. MISCAN-Colon, the CRC version of the MISCAN model, was developed in collaboration with the U.S. National Cancer Institute and experts in the field of CRC to assess the effect of different interventions on CRC. A detailed description of the model and the data sources that inform the quantification of the model can be found in the model appendix, in previous studies performed with the model[75-77] and in a standardized model profile.[78] In brief, the MISCAN-Colon model simulates the relevant biographies of a large population of individuals from birth to death, first without screening and subsequently with the changes that would occur under the implementation of a screening program. CRC arises in this population according to the adenoma-carcinoma sequence.[22, 23] More than one adenoma can occur in an individual and each can independently develop into CRC. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (≥ 10 mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage there is a chance of the cancer being diagnosed because of symptoms. The survival after clinical diagnosis depends on the stage of the cancer. The model also simulates when screening interrupts the development of CRC. With screening, adenomas may be detected and removed and cancers may be found, usually in an earlier stage than with clinical diagnosis. In this way screening prevents CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening.

The validity of the model is based on observational data before the introduction of screening, such as clinical incidence and mortality from CRC[135] and the size distribution of adenomas in autopsy studies.[174-183] The model has further been validated using the results of large (randomized) screening and surveillance studies, such as the CoCap sigmoidoscopy study,[75] the Minnesota Colon Cancer Control Study,[75] and the National Polyp Study.[184] Finally, the model was able to explain observed incidence and mortality trends in the U.S. when accounting for risk factor trends, screening practice and chemotherapy treatment.[185]

Study population

We used the natural history model to estimate the distribution of underlying disease for the 50-year old U.S. population in 2008 in terms of the presence, location, size, and type (adenoma vs. preclinical cancer) of lesions. We conducted the analysis of the effect of different screening strategies among a cohort of 10 million individuals beginning at age 50. The cohort was followed for life.

Scenarios

We evaluated three different treatment scenarios: “Past”, “Present” and “Near-future”. For the “Past scenario”, we assumed CRC survival and treatment costs as observed between 1990 and 1994. For the “Present scenario”, survival and treatment costs of 1998-2003 were assumed. Finally, for the “Near-future” we assumed improved survival and increased treatment costs over the 1998-2003 levels, based on the most recent clinical trial results.

Screening strategies

The screening strategies included the base-case strategy of no screening as well as 5 CRC screening strategies as recommended by the American Cancer Society and the Multi-Society Task Force[71] and the U.S. Preventive Services Task Force[210], either consisting of:

- annual fecal occult blood test (FOBT) with unrehydrated Hemoccult II
- annual immunochemical FOBT (FIT)
- 5-yearly sigmoidoscopy
- 10-yearly colonoscopy
- annual Hemoccult II in combination with 5-yearly sigmoidoscopy

In all scenarios screening began at age 50 and was discontinued after age 80.

Follow-up, surveillance, and adherence

We assumed that any individual with a positive FOBT was referred for a follow-up colonoscopy. For flexible sigmoidoscopy, we assumed that all detected polyps were biopsied and any person with an adenomatous polyp was referred for a follow-up colonoscopy. For the year in which both FOBT and flexible sigmoidoscopy were due, the FOBT was performed first and if positive, the subject was referred for colonoscopy. Flexible sigmoidoscopy was only done for those with a negative FOBT. Subjects with a negative follow-up colonoscopy returned to the specific screening program. If adenomas were detected on colonoscopy then the individual went to surveillance with colonoscopy per the 2006 guidelines from the joint publication of the U.S. Multi-Society Task Force and the American Cancer Society.[192] All individuals found with one or two adenomas that were both less than 10 mm in size underwent colonoscopy surveillance every 5 years. Individuals with at least one adenoma greater than or equal to 10 mm in size or with 3 or more adenomas underwent colonoscopy surveillance every 3 years. When the surveillance colonoscopy was normal or only detected one or two adenomas of size <10 mm, the next surveillance colonoscopy was at 5 years.

We assumed that all individuals were 100% adherent with screening, follow-up, and surveillance procedures. We specified a stop age of 80 years for screening (i.e. final screening at age 80) but allowed all individuals with an adenoma detected to continue to have surveillance colonoscopies until a diagnosis of CRC or death from other causes. All simulated individuals were followed until death.

CRC screening test characteristics

The assumptions for sensitivity and specificity of the CRC screening tests (Appendix Table 1 to this chapter) were based on the literature review conducted for the Agency for Health Care Research and Quality.[42] The lack of specificity for sigmoidoscopies and colonoscopies reflected the fact that in respectively 8% and 10% of persons without adenomas additional costs were induced because of biopsy, removal and pathology of non-adenomatous polyps. The rate of serious nonfatal complications was assumed to be 2.4 per 1000 colonoscopies.[58, 187-189] The rate of fatal events was assumed 0.1 per 1000 colonoscopies.[190]

Survival estimates

Survival estimates by stage for the "Past" and "Present scenarios" were obtained from the SEER database for diagnosed cases from 1990 to 1994 and 1998 to 2003 respectively.[211] For 1998-2003 a maximum of 6-years survival estimates were available. We used the period-estimation feature in SEER-Stat to estimate longer-term survival in this period. Survival estimates for the "Near-future scenario" were derived by using the hazard ratios for median survival from clinical trials[66] and applying them to the 1998-2003 stage-specific relative survival rates. Figure 5.1 contains a summary of relative survival estimates by stage and scenario used in this analysis.

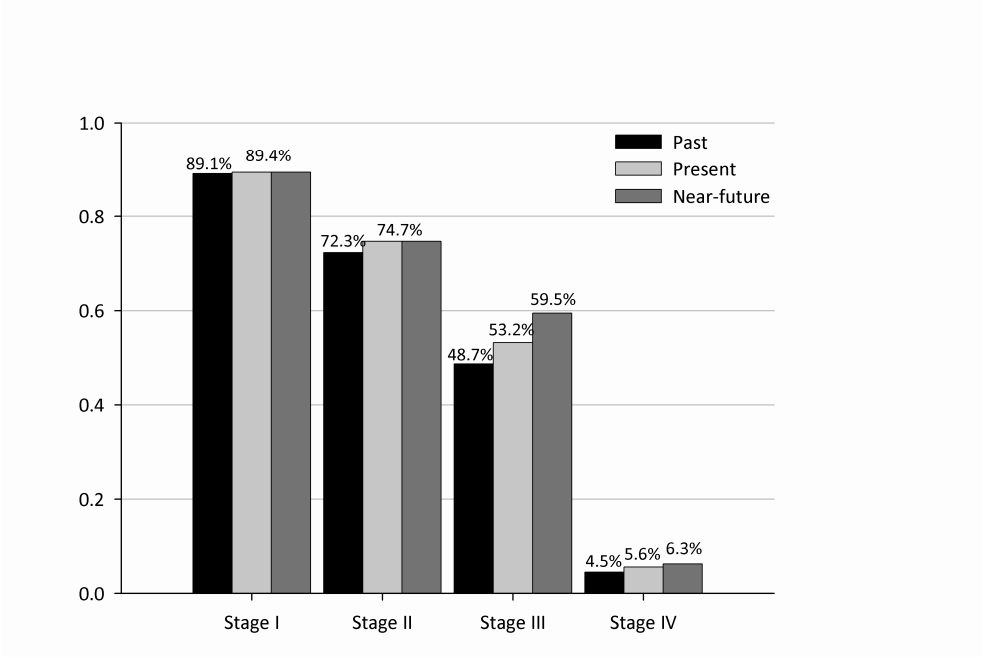

Figure 5.1: 10-year relative survival by stage and time period scenario, used as inputs for the MISCAN-Colon model

Cost inputs

The costs of CRC treatment for the "Past" and "Present scenarios" were derived from comparison of costs for CRC cases relative to those of matched controls in the SEER-Medicare files in 1990-1994 and 1998-2003 respectively.[191, 212] Costs of care were divided into three clinically relevant phases - initial, continuing and terminal care. The initial phase was defined as the first 12 months (6 months for "Past scenario" in concordance with cost data)[212] following 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 of care. For patients surviving less than 24 months after diagnosis, the final 12 months of observation and costs of care were allocated to the terminal phase, because the care for patients with short survival is more similar to the last year of life phase than to the initial phase. The remainder of survival time was allocated to the initial phase, with no contribution to the continuing phase. Treatment cost data was updated to 2007 dollars using the medical care component of the Consumer Price Index.

The treatment costs in the "Near-future scenario" were based on the "present scenario" costs and the differences in drug prices as presented by Schrag.[206] In the "Near-future scenario", we assumed that stage IV disease was initially treated with 5-FU in combination with oxaliplatin (FOLFOX). In the "Present scenario", stage IV disease was treated with 5-FU in combination with irinotecan (FOLFIRI). The difference in drug costs between FOLFIRI and FOLFOX is approximately $2,500 per cycle.[206] We assumed six drug cycles in the first year of treatment. This means that initial treatment for stage IV was $15,000 more expensive in the "Near-future scenario" than in the "Present scenario". Because FOLFOX has been proven effective for stage III as well, we assumed the same initial treatment and thus treatment costs for stage III as for stage IV. When dying of CRC (irrespective of the original stage of diagnosis), we assumed that six cycles of bevacizumab were added as second line treatment, making terminal treatment $60,000 more expensive in the "Near-future scenario" than in the "Present scenario". For the other phases the cost estimates were unchanged. The final cost inputs used in the model are summarized in Figure 5.2.

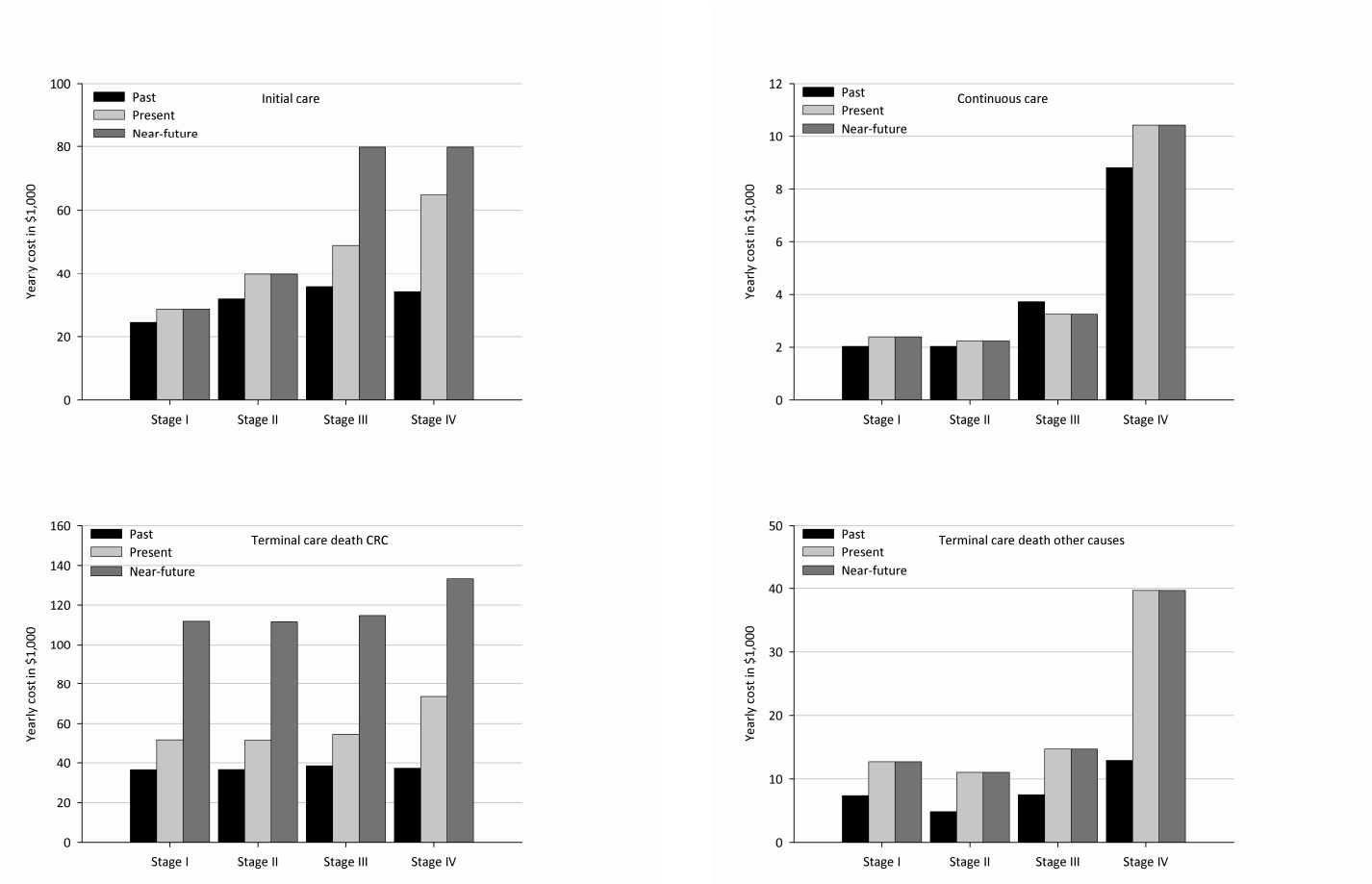

Figure 5.2: Unit costs in 2007 U.S.$ for CRC treatment by stage, phase of care and scenario, used as inputs for the MISCAN-Colon model[191, 212]

Table 5.1 shows unit costs for screening. These were based on Medicare payments of 2007 for procedures and tests associated with CRC screening and complications of screening, including beneficiary co-pays.[42] The unit costs of treatment of complications were based on the relevant Diagnosis Related Group (DRG) codes.[42]

Table 5.1: Unit costs in 2007 U.S.$ for screening and complications, used as inputs for the MISCAN-Colon model[42]

Screening test	Cost, $
Guaiac Hemoccult (II or SENSA)	4.54
Immunochemical fecal occult blood test (FIT)	22.22
Flexible sigmoidoscopy	160.78
Flexible sigmoidoscopy with biopsy	348.19
Colonoscopy without polypectomy	662.00
Colonoscopy with polypectomy or biopsy	846.00
Treatment of complications with screening	**Cost, $**
Perforation	12,446
Serosal burn	5,208
Bleed with transfusion	5,208
Bleed without transfusion	320

Outcomes

For each of the three scenarios, we calculated CRC incidence and stage distribution, and treatment and screening costs for the strategy of no screening, and the five competing screening strategies. All costs were discounted at an annual rate of 3%.

5.3 Results

Table 5.2 shows the number of CRC cases by stage, consisting of screen-detected and clinically diagnosed cases. Because the natural history of disease and the sensitivity of the screening tests were unchanged between the treatment scenarios, the numbers did not change between scenarios. According to the model, without screening, 66 of every 1000 50-year olds were clinically diagnosed with CRC in their lifetime. This corresponds to a 6.6% lifetime background risk. Almost 50% of the cases in the no screening situation presented with late-stage (stage III or IV) disease. With screening (assuming 100% adherence), many cancers were prevented, varying from 37% with annual Hemoccult II to 56% with 10-yearly colonoscopy. Screening improved the stage distribution, decreasing the number of CRC in stages II, III and IV, and increasing the number in stage I. For all

tests, screening resulted in a similar decrease in cancers in stages II-IV, while endoscopy prevented more stage I cases than FOBT.

Table 5.2: Simulated number of lifetime incident CRC cases per 1000 individuals by stage and screening strategy

Strategy	Stage I	Stage II	Stage III	Stage IV	Total	% Reduction*
No screening	12	23	15	16	66	n.a.
Hemoccult II	21	11	6	4	42	37
FIT	20	8	4	3	35	47
Sigmoidoscopy	14	10	6	5	34	49
Colonoscopy	14	8	5	3	30	56
Sigm + Hem II	16	8	4	3	31	53

n.a. = not applicable; Sigm + Hem II = combination of sigmoidoscopy and Hemoccult II.
* Compared to no screening.

From the "Past scenario" to the "Present" and "Near-future scenarios", savings from prevented cancers and cancer deaths by screening increased for all test strategies (Table 5.3, Figure 5.3). Appendix Table 2 to this chapter shows the calculation of treatment costs for all screening strategies in the "Near-future scenario". Because treatment costs per case mostly increased between the scenarios for stages III and IV (Figure 5.2) and the incidence reduction of cancers in these stages was similar for all test strategies (Table 5.2), the increase in total savings was also similar between tests. On average, total savings increased by 45% from the "Past" to the "Present scenario" and another 55% from the "Present" to the "Near-future scenario". Because screening costs remained stable over all scenarios (Table 5.3, Figure 5.3), the absolute total net costs of screening decreased at the same rate as the increase in absolute treatment savings. As a result, the lifetime treatment savings by screening with Hemoccult II (lifetime savings $1,387 per individual in the population), FIT ($1,744), sigmoidoscopy ($1,695) and the combination of sigmoidoscopy and FOBT ($1,919) became larger than the lifetime screening costs ($859, $1,633, $1,691 and $1,882 per individual in the population respectively) in the "Near-future scenario". For colonoscopy, the screening costs were larger than the treatment savings, but the remaining difference was small ($413 per individual in the population). The savings increased roughly from 40% of screening costs to 80%.

Table 5.3: Costs and savings of CRC screening by screening strategy and time-period scenario (lifetime average per individual in the population) - 3% discounted to age 50

Strategy	Scenario	Screening costs ($)	FU and surveillance costs ($)*	Treatment of CRC costs ($)	*Compared to no screening* Savings ($)†	Total net costs ($)‡
No screening	Past	0	0	1,927	-	-
	Present	0	0	2,542	-	-
	Near-future	0	0	3,507	-	-
Hemoccult II	Past	71	788	1,367	560	299
	Present	71	788	1,707	835	23
	Near-future	71	788	2,120	1,387	-528
FIT	Past	325	1,241	1,172	755	810
	Present	325	1,241	1,451	1,091	474
	Near-future	325	1,241	1,762	1,744	-179
Sigmoidoscopy	Past	773	918	1,111	816	875
	Present	773	918	1,407	1,135	555
	Near-future	773	918	1,811	1,695	-5
Colonoscopy	Past	1,501	858	990	937	1,422
	Present	1,501	858	1,239	1,304	1,055
	Near-future	1,501	858	1,561	1,946	413
Sigm + Hem II	Past	676	1,206	1,034	893	989
	Present	676	1,206	1,285	1,257	625
	Near-future	676	1,206	1,588	1,919	-36

Sigm + Hem II = combination of sigmoidoscopy and Hemoccult II.

* Including costs of diagnostic follow-up, surveillance tests and treatment of complications.

† Treatment costs without screening minus treatment costs for specific strategy.

‡ Sum of costs for specific strategy minus sum of costs without screening.

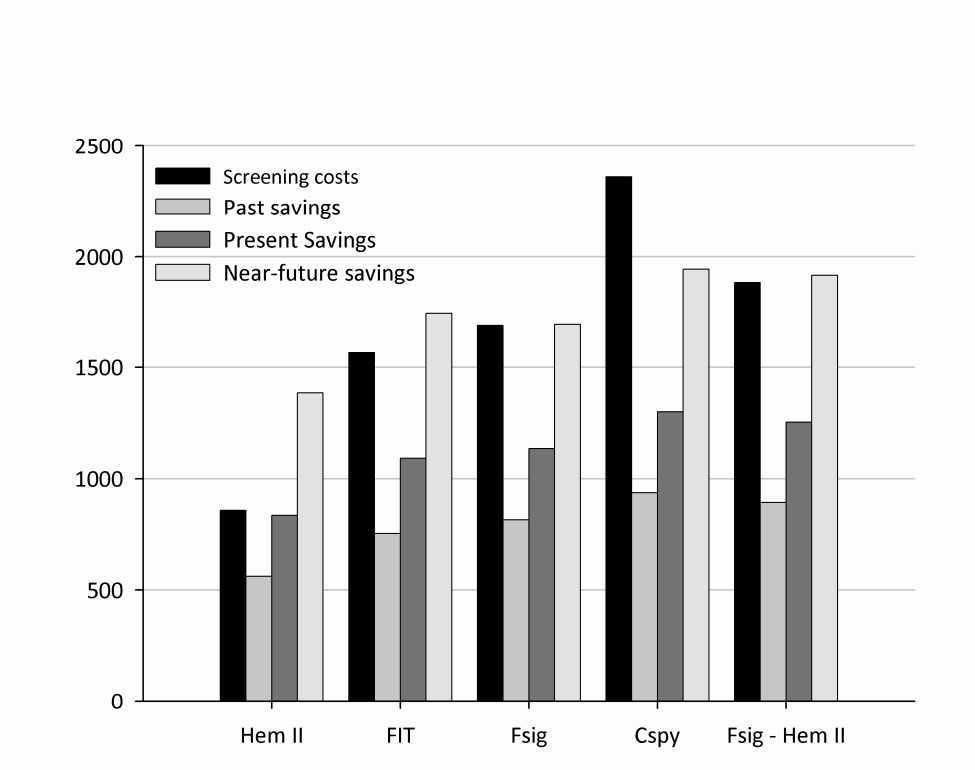

Figure 5.3: Screening costs (including diagnostic follow-up and surveillance) and treatment savings of CRC screening by screening strategy and time-period scenario (lifetime average per individual in the population) - 3% discounted to age 50.

5.4 Discussion

In this study, we found that the introduction of expensive chemotherapies, like oxaliplatin for stage III and IV and bevacizumab and cetuximab for metastatic disease ("Near-future") more than doubles treatment savings from screening for all test strategies. This makes annual FOBT screening with Hemoccult II and FIT cost-saving, as well as 5-yearly flexible sigmoidoscopy and the combination of sigmoidoscopy and FOBT. Colonoscopy did not become cost-saving, but the total net costs of this strategy also decreased substantially. Because colonoscopy screening reduces CRC incidence most, we had anticipated that increased treatment costs would have the most impact on savings from colonoscopy. Although savings are indeed the largest with colonoscopy screening, the difference with FOBT, for example, in this respect is modest. The reason is that the additional incidence reduction from colonoscopy screening is mostly in stage I cases, for which treatment costs have risen only slightly.

The crucial assumption in this analysis is that treatment costs increase rapidly over time, while screening costs remain stable. Observations in the recent past confirm this assumption. From 1990-1994 to 1998-2003, treatment costs per case have increased by up to 200% depending on the stage

of disease,[191, 212] while unit screening costs have not increased.[42, 209] The assumed increase in treatment costs from the "Present" to the "Near-future scenario" used for our model is uncertain. We assumed a lower increase than the observed increase from the "Past" to the "Present scenario". For the "Near-future" scenario, we have accounted for differences in price between the current chemotherapies (5-FU and FOLFIRI) and newly available chemotherapies (FOLFOX and bevacizumab). Besides chemotherapy, other therapies such as radiotherapy for rectal cancer, and extensive surgery for metastatic disease, continue to become more widely available, further increasing treatment costs and survival. These other therapies were not included in the current study. We may therefore have underestimated the increase in treatment costs from the "Present" to the "Near-future scenario". On the other hand, all patients with stage III and IV disease were assumed to receive the new chemotherapies in the "Near-future", while elderly patients with co-morbidities probably will not get the full dose or will receive no chemotherapy at all. This would limit the increase in treatment costs and survival. Because in the "Present scenario" the treatment savings from FOBT screening are already close to the screening costs, the conclusion that CRC screening will be cost-saving is robust to these uncertainties.

The CRC treatment costs have become a moving target because of the rapidly evolving chemotherapy standard. We used for the "Present scenario" the most recent, 1998-2003, cost estimates from Medicare. These costs have in the mean time already increased considerably, but data to measure this increase are not available yet. Also, the treatment cost in our "Near-future scenario" are likely to become conservative, because the second-line treatment of bevacizumab for recurrent disease is already being investigated as first-line treatment for stage IV disease, and even as adjuvant therapy for stage III and advanced stage II disease. These developments will only further increase the treatment savings from screening. By using different cost value inputs, additional savings from screening with these newer chemotherapy standards can be calculated (see Appendix Table 2 to this chapter).

Of course the new chemotherapies will not only increase costs but also decrease CRC mortality, by postponing or sometimes even preventing CRC death. Because of this better survival, fewer people die of CRC and less life-years are to be gained by screening. Improved survival was incorporated in our analysis, but its effect on life-years gained by screening turned out to be minimal. The shifting balance between screening costs and treatment savings of CRC screening with the introduction of new chemotherapies reflects the higher costs per life-year saved of these new treatments. Generally, cost-effectiveness thresholds for treatments are much higher than for secondary prevention. It is therefore good to realize that with the introduction of expensive chemotherapies with high costs per life-year gained, secondary prevention becomes more and more cost-effective.

We assumed 100% adherence with screening, diagnostic follow-up and surveillance. Although unrealistic, this assumption does not influence the results of our analysis. Incomplete adherence to screening will decrease screening costs and treatment savings proportionally, which means that the relative difference between screening costs and treatment savings is not influenced. In case of occasional adherence to screening (some but not all screening rounds are attended by an individual), the savings from screening will even increase somewhat more than the screening costs.

Three earlier studies concluded that sigmoidoscopy and colonoscopy screening can be cost-saving.[77, 213, 214] In the present study, colonoscopy screening was not cost-saving, because of the higher costs

assumed for colonoscopy. The cost estimates in this study are based on Medicare reimbursement rates, whereas in the other studies, estimates reflect (European) costs in organized screening programs. In Europe, the newly available chemotherapies are as expensive as in the U.S.,[215] while the screening costs are lower.[213, 214, 216] This means that savings from screening in Europe would be comparable to those in the U.S., while the screening costs are lower. For example, a screening colonoscopy in Germany costs approximately one-third of one in the U.S. according to the reimbursement rate.[214] With these costs, colonoscopy screening would become cost-saving, even more so than Hemoccult II screening. The FIT test mostly used in Europe (OC-Hemodia Latex, Eiken Chemical Co., Tokyo, Japan) costs approximately the same as a Hemoccult II test.[217] This would make FIT testing even more cost-saving than currently estimated.

In conclusion, the increasingly costly management of CRC approximately doubles the treatment savings from screening. As a consequence, FOBT, sigmoidoscopy and the combination of sigmoidoscopy and FOBT become cost-saving and colonoscopy screening nearly so. The results are based on U.S. data, but are also applicable to the European situation. For these reasons, screening is not only desirable for governments and insurance companies to reduce CRC incidence and mortality, but it will also help to contain the raise in costs for the management of CRC.

Appendix Table 1 to chapter 5: Test characteristics used in the MISCAN model

Test characteristic	Value	Source
Sensitivity Hemoccult II*	Dependent on stage of disease: Adenoma 1-5 mm: 2% Adenoma 6-9 mm: 5% Adenoma ≥ 10 mm: 12% Cancer: 40%	Literature review[42]
Sensitivity FIT*	Dependent on stage of disease: Adenoma 1-5 mm: 5% Adenoma 6-9 mm: 10% Adenoma ≥ 10 mm: 22% Cancer: 70%	Literature review[42]
Sensitivity sigmoidoscopy*,†	Dependent on stage of disease: Adenoma 1-5 mm: 75% Adenoma 6-9 mm: 85% Adenoma ≥ 10 mm: 95% Cancer: 95%	Back-to-back colonoscopy studies[53]
Sensitivity colonoscopy*	Dependent on stage of disease: Adenoma 1-5 mm: 75% Adenoma 6-9 mm: 85% Adenoma ≥ 10 mm: 95% Cancer: 95%	Back-to-back colonoscopy studies[53]
Specificity‡	Hemoccult II: 98% FIT: 95% Sigmoidoscopy: 92% Colonoscopy: 90%	Literature review[42]
Reach sigmoidoscopy	80% reach junction of sigmoid and descending colon, 40% reach splenic flexure	Kaiser Permanente study[218]
Cecal intubation rate with colonoscopy	95%	General practice[219, 220] and guidelines[221]
Complication rate with colonoscopy Perforation Serosal burn Bleed with transfusion Bleed without transfusion	2.4 per 1000 colonoscopies 0.7 per 1000 0.3 per 1000 0.4 per 1000 1.1 per 1000	Organized screening programs[187-189] and general practice[58, 222]

Appendix Table 1 to chapter 5 continued

Test characteristic	Value	Source
Fatal complication rate with colonoscopy	0.1 per 1000 colonoscopies	Prospective endoscopy study[190]
Perforation rate with sigmoidoscopy	0.02 per 1000 sigmoidoscopies	Sigmoidoscopy study[222]
Fatal complication rate with sigmoidoscopy	0	Sigmoidoscopy study[222]

FIT = immunochemical fecal occult blood test.

* Sensitivity is provided per individual for stool-based tests and per lesion for endoscopy tests.

† Test characteristics for sigmoidoscopy only apply to the distal colon and rectum.

‡ The lack of specificity with colonoscopy and sigmoidoscopy screening reflects the detection of non-adenomatous lesions. With colonoscopy these non-adenomatous lesions are removed and therefore induce polypectomy costs. With sigmoidoscopy the presence of non-adenomatous lesions induces biopsy costs (in case of sigmoidoscopy with biopsy) or results in referral for diagnostic colonoscopy (in case of sigmoidoscopy without biopsy).

Appendix Table 2 to chapter 5: Cost estimates and simulated number of life-years for CRC care per 1000 individuals for the near-future scenario by stage, phase of care and screening strategy

Strategy	Initial care*				Continuous care*				Terminal care, death CRC*				Terminal CRC care, death other causes*				Treatment of CRC costs ($)† (x 1000)
	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	Stage I	Stage II	Stage III	Stage IV	
Yearly cost inputs	28,668	39,700	79,801	79,801	2,395	2,237	3,249	10,419	111,935	111,712	114,776	133,522	12,703	11,035	14,708	39,679	
Life-years																	
No screening	5.6	10.0	6.6	3.2	65.2	93.9	59.9	11.0	0.5	2.3	2.6	4.9	3.8	6.2	3.5	0.8	3,477
Hem II	11.4	4.8	2.7	0.9	137.7	53.8	31.6	4.0	1.0	1.2	1.1	1.4	7.0	2.9	1.5	0.2	2,111
FIT	11.1	3.6	1.9	0.6	137.3	42.1	24.7	3.0	0.9	0.9	0.8	1.0	6.7	2.2	1.1	0.2	1,756
Fsig	7.0	4.5	2.8	1.0	85.3	51.0	31.7	4.5	0.6	1.1	1.1	1.6	4.5	2.7	1.5	0.3	1,802
Cspy	7.3	3.7	2.2	0.7	88.7	43.6	27.1	3.4	0.6	0.9	0.9	1.1	4.7	2.2	1.2	0.2	1,554
Fsig + Hem II	8.7	3.5	2.0	0.6	107.0	42.0	25.3	3.0	0.7	0.9	0.8	1.0	5.4	2.2	1.1	0.2	1,582

* Costs for care were divided into three clinically relevant phases of care - initial, continuing 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 continuing phase was defined as the period between the initial and last year of life phases of care. The terminal care phase of CRC patients was further subdivided into terminal care preceding CRC death and terminal care preceding death of other causes. 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. The remaining time was allocated to the initial phase, with no contribution to the continuing phase.

† Average costs for CRC treatment per 1000 individuals in the population, excluding costs of diagnosis of symptom detected cases. Calculated as sum of yearly cost inputs times life-years with care by phase and stage of disease For example treatment costs in No screening strategy are equal to: 5.6*28,668 + 10.0*39,700 + 6.6*79,801 + 3.2*79,801 + 65.2*2,395 + 93.9*2,237 + 59.9*3,249 + 11.0*10,419 + 0.5*111,935 + 2.3*111.712 + 2.6*114,776 + 4.9*133,522 + 3.8*12,703 + 6.2*11,035 + 3.5*14,708 + 0.8*39,679 = 3,477,000. This number is slightly different from the number reported in Table 3 in the main text (3,507,000) that also includes the costs for diagnosis of CRC (29,000).

Chapter 6: Individualizing colonoscopy screening by sex and race

Abstract

Background: There is increasing discussion whether colorectal cancer (CRC) screening guidelines should be individualized by sex and race.

Objectives: To determine individualized colonoscopic screening guidelines by sex and race for the average-risk population and to compare the cost-effectiveness of this approach to that of uniform guidelines for all.

Design: We used the MISCAN-Colon microsimulation model to estimate life expectancy and lifetime CRC screening and treatment costs in a U.S. cohort of black and white men and women at average risk for CRC. We compared the base-case strategy of no screening and 3 competing colonoscopy strategies: (1) the currently recommended ''uniform 10-yearly colonoscopy from age 50 years,'' (2) with a shorter interval ''uniform 8-yearly colonoscopy from age 51 years,'' and (3) ''individualized screening according to sex and race.''

Results: The base-case strategy of no screening was the least expensive, yet least effective. The uniform 10-yearly colonoscopy strategy was dominated. The uniform 8-yearly colonoscopy and individualized strategies both increased life expectancy by 0.0433-0.0435 years per individual, at a cost of $15,565-$15,837 per life-year gained. In the individualized strategy, blacks began screening 6 years earlier, with a 1-year shorter interval compared to whites. The individualized policies were essentially the same for men and women, because the higher CRC risk in men was offset by their shorter life expectancy. The results were robust for changes in model assumptions.

Conclusions: The improvements in costs and effects of individualizing CRC screening on a population level were only marginal. Individualized guidelines, however, could contribute to decreasing disparities between blacks and whites. The acceptability and feasibility of individualized guidelines, therefore, should be explored.

6.1 Introduction

For the average-risk population, the U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society recommend starting colorectal cancer (CRC) screening at the age of 50 years, with an identical menu of screening options for men and women of all races.[71, 107] There are separate guidelines for individuals at increased risk because of a family history of CRC, a genetic predisposition (e.g., familial adenomatous polyposis and hereditary nonpolyposis CRC), or a personal history of CRC, adenomas, or inflammatory bowel disease. The U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society recommend that these individuals have colonoscopy screening at earlier ages and with higher frequency than the general population.[71, 107] Race or sex is not used as a basis for modifying recommendations.

Given the differences in CRC risk by sex, race, and ethnicity, debate has arisen whether screening guidelines should be individualized accordingly.[223] The American College of Gastroenterology advocates that screening should start earlier in blacks because of the higher incidence and younger age at presentation of CRC in this population subgroup.[224] During the period 1997 to 2001,[225] black men had the highest age-specific CRC mortality, whereas white women had the lowest rate in the United States (Figure. 6.1). The 4 curves in Figure 6.1 become nearly indistinguishable when the rates for blacks are shifted 5 years later compared to whites (including Hispanics) and 5 years earlier for women compared to men.[225] The disparity seems to support individualizing age of screening initiation by sex and race.

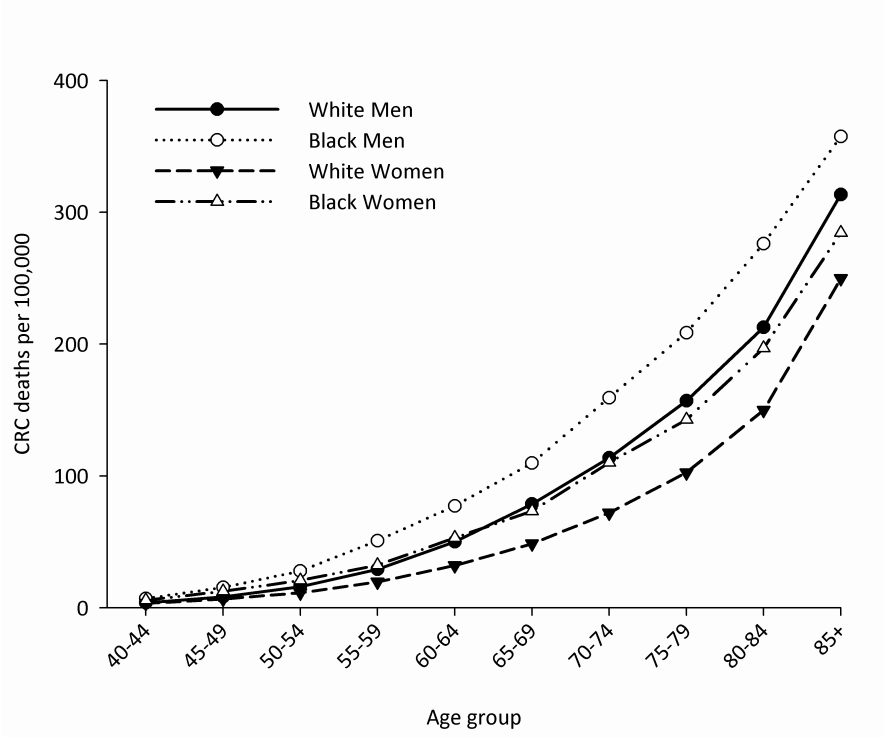

Figure 6.1: U.S. age-specific colorectal cancer mortality rates per 100,000 white men, black men, white women, and black women, 1997-2001.[225]

Next to mortality, other determinants should be considered for individualizing screening guidelines. Important determinants would be life expectancy, incidence, stage distribution, survival, and costs. A simulation approach can take all these aspects into account and estimate costs and life-years gained, which is a commonly used summary measure for the benefit of cancer screening,[226] for different screening strategies. In this study, we used the MISCAN-Colon microsimulation model to determine individualized colonoscopy screening guidelines by sex and race for the average-risk population and compare their cost-effectiveness to uniform guidelines with the same screening ages and interval for all.

6.2 Materials and methods

We used the MISCAN-Colon microsimulation model to determine the most cost-effective approach for colonoscopy screening in the average-risk population. The base-case strategy was no screening. This strategy was compared to 2 uniform and 1 individualized colonoscopy strategies.

MISCAN-Colon microsimulation model

The MISCAN microsimulation model was developed at the Department of Public Health, Erasmus MC, the Netherlands, and has been used to evaluate breast, cervical, colon, and prostate cancer screening. MISCAN-Colon, the CRC version of the MISCAN model, was developed in collaboration with the U.S. National Cancer Institute (NCI) and experts in the field of CRC to assess the effect of different interventions on CRC. A graphical representation of the natural history in the model is given in Figure 1.8, and the main natural history assumptions in the model are listed in Table 6.1. A detailed description of the model and the data sources that informed the quantification of the model can be found in the model appendix, in previous publications,[76, 77] and also in a standardized model profile.[78] In brief, the MISCAN-Colon model simulates the relevant biographies of a large population of individuals from birth to death, first without screening and subsequently with the changes that would occur under the implementation of screening. CRC arises in this population according to the adenoma-carcinoma sequence.[22, 23] More than 1 adenoma can occur in an individual and each adenoma can independently develop into CRC. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (≥ 10 mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) will eventually become a clinical cancer. Diagnosis of cancer occurs on average 10 years after the manifestation of the adenoma from which it developed. This development competes with death from other causes. A preclinical cancer may progress from stage I to stage IV. In every stage, there is a chance of the cancer being diagnosed because of symptoms. The cure rate and survival after diagnosis without cure depend on the stage of the cancer. The model also simulates how screening can interrupt the development of CRC and how it improves prognosis. With screening, adenomas may be detected and removed and preclinical cancers may be found, depending on sensitivity. In this way, screening may prevent CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life expectancy of the population with and without screening. We assumed the sensitivity of colonoscopy is 75% (95% CI 70%-79%) for small adenomas (1-5 mm), 85% (95% CI 80%-92%) for medium adenomas (6-9 mm), and 95% (95% CI 92%-99%) for large adenomas (≥ 10 mm) and cancers, based

on back-to-back colonoscopy studies.[53] We assumed a specificity of 90% of colonoscopy. This percentage was equal to 1 minus the 10% of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after colonoscopy. Specificity was assumed to be independent of the screening round. We assumed a cecal intubation rate of 95%.[219-221] Harms associated with colonoscopy were assumed to be perforations (0.7 per 1000 colonoscopies), serosal burns (0.3 per 1000), bleeds that require transfusion (0.4 per 1000), and bleeds that do not require transfusion (1.1 per 1000), all of which can occur with or without polypectomy.[58, 187-189] We assumed that fatal events occur at a rate of 1 per 10,000 colonoscopies.[190]

Table 6.1: Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2	Fit to multiplicity distribution of adenomas in colonoscopy and autopsy studies:[197, 198, 227-229] Age 60: 1 or more 20% 2 or more 6% 3 or more 2% Age 90: 1 or more 37% 2 or more 17% 3 or more 9%
Adenoma incidence per year	Age, gender and race dependent	Fit to adenoma prevalence in autopsy and colonoscopy studies of 15% in age group 50-59 to 33% in age group 70+,[197, 198, 227-229] and to cancer incidence per 100,000 in 1997-2001 in SEER registry:[135]

Age:	White		Black	
	Men	Women	Men	Women
0-29 years:	0.0%	0.0%	0.0%	0.0%
30-39 years:	0.2%	0.1%	0.2%	0.2%
40-44 years:	0.4%	0.4%	1.0%	0.6%
45-49 years:	0.9%	0.6%	1.3%	1.2%
50-54 years:	1.6%	1.0%	2.0%	1.5%
55-59 years:	2.9%	1.8%	3.0%	2.3%
60-64 years:	3.2%	2.2%	3.3%	2.4%

	White		Black	
Age	Men	Women	Men	Women
0-20:	0.1	0.1	0.1	0.0
20-24:	0.7	0.6	0.4	1.3
25-29:	1.5	1.8	2.1	1.9
30-34:	3.6	3.5	3.1	3.8
35-39:	7.1	5.8	8.5	8.1
40-44:	12.9	11.1	17.5	14.8
45-49:	26.3	22.2	36.9	33.1

Table 6.1 continued

Model parameter	Value				Source				
65-69 years:	3.2%	2.2%	3.7%	2.5%	50-54:	51.5	37.8	74.1	57.3
70-74 years:	3.2%	2.3%	4.3%	2.5%	55-59:	91.4	60.5	111.4	97.3
75-84 years:	1.8%	1.2%	1.3%	1.0%	60-64:	150.0	103.5	198.4	140.1
85-100 years:	1.4%	1.1%	1.1%	0.5%	65-69:	226.5	151.8	231.9	193.9
					70-74:	302.8	212.8	315.3	237.8
					75-79:	378.1	279.9	435.7	309.0
					80-84:	457.4	338.4	488.1	361.2
					85-100:	500.9	391.6	469.1	335.6
Probability that a new adenoma is progressive	Dependent on age at onset: 0-65 years: 14% 65-100 years: linearly increasing from 14% to 96%				Fit to adenoma prevalence in autopsy studies,[197, 198, 227-229] cancer incidence in SEER registry in 1978.[135]				
Regression of adenomas	No significant regression of adenomas				Expert opinion				
Mean duration of development of progressive adenomas to clinical cancer	20 years				Expert opinion*				
Mean duration of preclinical cancer	3.6 years				Estimated from cancer detection rate at first screening and background cancer incidence in FOBT trials.[28, 81]				
Mean duration of adenoma	16.4 years				20 years - 3.6 years				
Percent of non-progressive adenomas that stay 6-9mm	50%				Fit to size distribution of adenomas in autopsy studies:[197, 198, 227-229] 1-5mm: 56% 6-9 mm: 24%				

Table 6.1 continued

Model parameter	Value				Source
					≥ 10 mm: 20%
Percent of non-progressive adenoma that become 10mm or larger	50%				Fit to size distribution of adenomas in autopsy studies:[197, 198, 227-229] 1-5mm: 56% 6-9 mm: 24% ≥ 10 mm: 20%
Percent of cancers that develops from 6-9mm adenoma and from ≥ 10mm adenoma	30% of cancer develops from 6-9 mm, 70% from ≥ 10mm				Expert opinion
Localization distribution of adenomas and cancer	Dependent on gender and race:				Directly estimated from SEER 1997-2001.[135]
	White		Black		
	Men	Women	Men	Women	
Rectum:	22%	17%	19%	15%	
Rectosigmoid junction: Sigmoid colon:	9%	7%	8%	8%	
Descending colon:	23%	21%	20%	20%	
Transverse colon (incl flexures):	5%	4%	6%	6%	
Ascending colon:	14%	15%	16%	16%	
Cecum:	12%	14%	14%	15%	
	16%	21%	18%	21%	
10-year survival after clinical diagnosis of CRC	Dependent on stage, gender and race:				Directly estimated from SEER 1997-2001.[135]
	White		Black		
	Men	Women	Men	Women	
Stage I:	95%	96%	71%	89%	
Stage II:	76%	80%	73%	68%	

Table 6.1 continued

Model parameter	Value				Source
Stage III:	58%	52%	40%	43%	
Stage IV:	7%	4%	5%	3%	
Sensitivity colonoscopy					Van Rijn et al,[53] 2007
Adenoma 1-5 mm:	75%				
Adenoma 6-9 mm:	85%				
Adenoma ≥ 10 mm:	95%				
Cancer:	95%				
Cecal intubation rate with colonoscopy	95%				Aslinia et al,[219] 2006; Cotterill et al,[220] 2005; Rex et al,[221] 2002.
Complications with colonoscopy	Per 1000 colonoscopies:				Levin et al,[58] 2006; Lieberman et al,[187] 2000; Pox et al,[188] 2007; Regula et al,[189] 2006; Jentschura et al,[190] 1994.
Perforations	0.7				
Fatal perforations	0.1				
Serosal burn	0.3				
Bleeds with transfusion	0.4				
Bleeds without transfusion	1.1				

* To be estimated from randomized controlled endoscopy trials, data not yet available.

The validity of the model is based on observational data before the introduction of screening, such as clinical incidence and mortality from CRC[135] and the size distribution of adenomas in colonoscopy and autopsy studies.[197, 198, 227-229] The external validity has further been tested on the results of large (randomized) screening and surveillance studies, such as the Minnesota Colon Cancer Control Study,[75] the Colon Cancer Prevention Program (CoCap) sigmoidoscopy study,[75] and the National Polyp Study.[184] Also, 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.[185]

In this study, the model was used to simulate a U.S. cohort born in 1967, subdivided by sex and race (blacks and whites, including Hispanics).[230] Age-specific adenoma onset, distribution of cancer localization over the colorectum, distribution of CRC stages, stage-specific CRC survival, and all-cause mortality rates were adjusted for all sex and race combinations to reflect observed CRC incidence and mortality and other-cause mortality in the period 1997 to 2001.[135] Adenoma and cancer progression were assumed to be the same for all sexes and races. Subsequently, the model was used to predict costs and life expectancy for different screening strategies.

According to our model, the current recommendation of colonoscopy screening every 10 years from age 50 years was not optimally cost-effective, although it was close. To enable a fair and interpretable comparison between uniform and individualized guidelines, we also determined a cost-effective uniform colonoscopy strategy. To obtain this cost-effective uniform strategy, we simulated more than 1000 colonoscopy screening policies that differed with respect to age to begin screening, screening interval, and total number of screenings. Policies that were more costly and less effective than other policies were ruled out as non-efficient by simple dominance. Policies that were more costly and less effective than a combination of other strategies were ruled out as non-efficient by extended dominance. Of the remaining policies (see Appendix Table 1 to this chapter), we selected the policy that was closest to the current recommendation with respect to the number of screenings and the age to begin screening as the alternative uniform strategy (the result was strategy 2).

To obtain individualized guidelines, we first determined the cost-effective colonoscopy policies by population subgroup, as described above (Appendix Tables 2-5 to this chapter). For each cost-effective policy, we calculated the incremental cost-effectiveness ratio, defined as the additional cost of a specific policy divided by its additional clinical benefit compared to the closest less-expensive cost-effective policy. Next, we combined cost-effective policies, one for each population subgroup, with the same threshold for the incremental cost-effectiveness ratio.[231, 232] For each of the resulting individualized strategies, the costs and life-years of the 4 population subgroups were summed. The strategy with total costs closest to that of the alternative uniform strategy was used as the individualized strategy (the result was strategy 3).

Base-case

The base-case for the analysis was the absence of screening for CRC. All diagnoses of CRC occurred because of symptoms, after which patients received treatment according to current practice.

Competing screening strategies

1. Uniform 10-yearly colonoscopy at age 50 years. In this strategy, all individuals were offered colonoscopy screening at age 50 years and every 10 years thereafter up to age 80 years, according to guidelines.[107]

2. Uniform 8-yearly colonoscopy at age 51 years. In this strategy (resulting from the modeling analysis described before), all individuals were offered colonoscopy screening at age 51 years and every 8 years thereafter up to age 75 years.

3. Individualized screening according to sex and race. In this strategy, each population subgroup (black and white men and women) was allowed to have a different colonoscopy policy. The policies, which resulted from the modeling analysis described before, were
    a. White men: 4 screenings from age 53 to 74 years every 7 years.
    b. Black men: 5 screenings from age 47 to 75 years every 7 years.
    c. White women: 4 screenings from age 53 to 77 years every 8 years.
    d. Black women: 5 screenings from age 47 to 75 years every 7 years.

As part of all simulated screening strategies, patients with adenoma (in whom adenomas had been detected and consequently removed) were kept under colonoscopy surveillance according to the guidelines of the U.S. Multi-Society Task Force on Colorectal Cancer.[192]

Costs

Screening costs were based on Medicare payments of 2007 for procedures and tests associated with CRC screening and complications of screening.[42] The costs of complications were based on the relevant Diagnostic Related Group codes.[42] The phase-specific costs of CRC treatment (Table 6.2, footnote *) were derived by comparing medical costs of CRC cases relative to matched controls in the SEER-Medicare files.[191] The results were reported in 2004 dollars and subsequently updated to 2007 dollars by using the medical care component of the Consumer Price Index. The final cost inputs used in the model are summarized in Table 6.2.

Table 6.2: Unit Costs in 2007 U.S. dollars (95% confidence interval) for screening and CRC treatment, used as inputs for the MISCAN-Colon model

Screening Costs[42]		CRC Treatment Costs[191]				
Procedure	Cost	Stage	Initial*	Continuous*	Terminal care, death CRC*	Terminal care, death other cause*
Colonoscopy	$662	I	$28,668 ($27,905-$29,432)	$2,395 ($2,179-$2,612)	$51,935 ($49,690-$54,181)	$12,703 ($10,533-$14,870)
Colonoscopy with polypectomy	$846	II	$39,700 ($38,876-$40,525)	$2,237 ($2,036-$2,440)	$51,712 ($49,989-$53,434)	$11,035 ($9214-$12,856)
CTC	Varied	III	$48,951 ($47,924-$49,976)	$3,249 ($2,966-$3,531)	$54,776 ($53,204-$56,348)	$14,708 ($11,993-$17,422)
Treatment of perforation	$12,446	IV	$64,801 ($62,420-$67,181)	$10,419 ($9,249-$11,590)	$73,522 ($71,800-$75,243)	$39,679 ($31,826-$47,532)
Treatment of serosal burn	$5,208					
Treatment of bleed with transfusion	$5,208					
Treatment of bleed without transfusion	$320					

* Costs for 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 following 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 last year of life phases of care. The terminal care phase of CRC patients was further subdivided into terminal care before CRC death and terminal care before death of other causes. Cause of death was identified by use of death certificate information in the SEER database. 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.

Outcomes

We projected lifetime costs and life expectancy for a cohort of 40-year old black and white men and women in the United States. Costs and future life-years were discounted at an annual rate of 3%.[233]

Sensitivity and uncertainty analysis

We performed a 1-way sensitivity and a multivariate uncertainty analysis on influential model assumptions:

- The assumption of a higher incidence of adenomas versus faster progression of adenomas, which explained the risk differences between population subgroups.
- The duration of the adenoma-carcinoma sequence.
- The CRC risk in blacks.
- Sensitivity, specificity, and complication rate of colonoscopy.
- Costs of colonoscopy, polypectomy, complications, and CRC treatment.

Because the focus of the analysis was to assess the cost-effectiveness of individualized guidelines compared to uniform guidelines, we restricted the sensitivity analysis to comparing strategies 2 and 3. In the 1-way sensitivity analysis, each parameter was varied from its original value to a low and high value. For colonoscopy sensitivity and treatment costs, these values were set at the boundaries of the 95% CIs. Ranges reported in the literature were used for colonoscopy reach;[187, 219, 234-240] specificity;[172, 187, 239, 241, 242] perforation rates;[170-172, 202, 209, 243-247] and the costs of colonoscopy, polypectomy, and complications.[49, 170-172, 202, 209, 241-247] The average duration between the manifestation of an adenoma and the diagnosis of CRC (base assumption 10 years) was decreased and increased by 50%, whereas the CRC risk in blacks was decreased and increased by 10%. In the multivariate uncertainty analysis, we simulated the uniform 8-yearly colonoscopy and individualized strategies 1000 times, with different sets of parameters. The test characteristic parameters (sensitivity, specificity, reach, and complication rate) were drawn from a beta distribution, with the mean equal to the base value. For the cost parameters and the CRC risk in blacks, we assumed lognormal distributions, with the median equal to the base value. For all parameters varied, the standard deviation was chosen such that the 95% probability mass overlapped with the low and high values used in the 1-way sensitivity analysis. In 50% of the runs, we assumed a duration of the development of CRC of 10 years, whereas half and double durations were used in 25% of the runs each. In 75% of the runs, we assumed that the difference in CRC risk between population subgroups was because of a different adenoma incidence, whereas, in 25%, we assumed the difference was caused by different adenoma progression rates. For each of the 1000 simulations, the difference in costs and life expectancy between the uniform 8-yearly colonoscopy strategy and the individualized strategy were plotted in a scatterplot.[248]

6.3 Results

The life expectancy and lifetime costs of the no screening, uniform 8-yearly colonoscopy, uniform 10-yearly colonoscopy and individualized strategies are displayed in Table 6.3. The no-screening strategy was the least expensive yet least-effective strategy. The uniform 8-yearly colonoscopy and individualized strategies both increased life expectancy by 0.0433-0.0435 years per individual at a cost of $15,565-$15,837 per life-year gained compared to no screening. The uniform 10-yearly colonoscopy strategy was weakly dominated by both the uniform 8-yearly strategy and the individualized strategy.

Life expectancy and costs for the uniform 8-yearly and individualized colonoscopy strategies by population subgroup are shown in Table 6.4. The increase in screening intensity in blacks with individualization resulted in 0.0080 years longer life expectancy in black men, whereas, in black women, the life expectancy increased by 0.0076 years. The redistribution of resources from lower-risk whites to higher-risk blacks, resulted in a higher starting age (2 years later), with individualization for whites and a slightly decreased life expectancy in this group by 0.0006 years for men and 0.0016 years for women.

Table 6.3: Results from cost-effectiveness analysis

Strategy	CRC cases/100,000 from age 40y to age 100y	CRC deaths/100,000 from age 40y to age 100y*	Life-expectancy at age 40y†	Lifetime per person cost for CRC screening and treatment after age 40y ($)†	ICER ($)†
No screening	5,712	2,027	22.3929	1,663	Base-case
Uniform 10-yearly colonoscopy	3,026	794	22.4340	2,310	Dominated
Uniform 8-yearly colonoscopy	2,901	751	22.4362	2,349	15,837
Individualized	2,882	739	22.4363	2,340	15,565

ICER = incremental cost-effectiveness ratio.

* Includes procedural deaths from colonoscopy complications.

† 3% discounted.

Table 6.4: Comparison of 3% discounted costs and life expectancy between the uniform 8-yearly colonoscopy and individualized strategies, by sex and race, and for the total population

Population subgroup	Uniform 8-yearly colonoscopy strategy			Individualized strategy			Difference in life-expectancy
	Uniform strategy	Costs ($)*	LE-40	Individualized strategy	Costs ($)*	LE-40	
White men	4 screenings, every 8y; age 51-75y	2,408	21.9418	4 screenings, every 7y; age 53-74y	2,361	21.9412	-0.0006
Black men	4 screenings, every 8y; age 51-75y	2,240	19.8791	5 screenings, every 7y; age 47-75y	2,582	19.8871	+0.0080
White women	4 screenings, every 8y; age 51-75y	2,314	23.4309	4 screenings, every 8y; age 53-77y	2,221	23.4293	-0.0016
Black women	4 screenings, every 8y; age 51-75y	2,299	21.9359	5 screenings, every 7y; age 47-75y	2,671	21.9435	+0.0076
Total population[†]		2,349	22.4362		2,340	22.4363	+0.0002

LE-40 = Life-expectancy at age 40y.

* Lifetime per person cost for CRC screening and treatment after age 40y.

[†] Average of results for population subgroups, weighted by size of population subgroup.

Sensitivity and uncertainty analysis

In the 1-way sensitivity analysis, we assessed the influence of model assumptions on the differences between uniform 8-yearly colonoscopy and individualized screening. In all analyses, both strategies were equivalent in costs and effects (Table 6.5). The difference in costs never exceeded $12, and the maximum difference in life-years gained was 0.0005 years. With a longer duration of the adenoma-carcinoma sequence of 30 years, the uniform 8-yearly strategy became most effective, which nullified the already very small advantage of individualized screening. Other influential model assumptions on effectiveness were the disparity in CRC risk, colonoscopy sensitivity, and reach, and whether disparities in incidence are caused by the difference in adenoma onset versus faster progression. Costs were mostly influenced by colonoscopy costs and the duration of the adenoma-carcinoma sequence.

For the multivariate uncertainty analysis, the results from 1000 simulations that compared the uniform 8-yearly colonoscopy and individualized strategies are shown in Figure 6.2. In all simulations, the uniform 8-yearly colonoscopy and individualized strategies remained equivalent in costs and effects. The median difference in life-years gained was 0.0002 life-years. The 25% and 75% percentiles of the increase in life-years gained from the individualized strategy compared to the uniform strategy was 0.0001 and 0.0002 life-years, respectively, whereas the 25% and 75% percentiles for the decrease in cost were $7.20 to $11.50. For blacks, the 25% and 75% percentiles of additional life-years gained were 0.0063 and 0.0079 years and of additional costs were $260 to $465. In 83% of the simulations, the individualized strategy was more effective and less costly than the uniform strategy. Uniform screening was more effective in 3% of simulations, at an incremental cost per life-year gained of $50,000 or less, and, in 7%, at costs of $100,000 or less.

Table 6.5: Results of 1-way sensitivity analysis: comparison of 3% discounted costs and life expectancy in the total population with the uniform 8-yearly colonoscopy and individualized strategies for different model assumptions

	Differences of the individualized strategy compared to the uniform 8-yearly colonoscopy strategy					
	Low value			High value		
Model parameter	Gain in LE	Costs ($)*	ICER	Gain in LE	Costs ($)*	ICER
Base assumptions	+0.0002	-9.09	Dominant	+0.0002	-9.09	Dominant
Fast progression of adenomas[†]	+0.0001	-7.89	Dominant			
Duration of adenoma-carcinoma sequence[§]	+0.0005	-10.11	Dominant	-0.0000	-6.66	$546,213[‡]
Risk blacks[§]	+0.0001	-6.67	Dominant	+0.0003	-9.40	Dominant
Reach colonoscopy[§]	+0.0003	-8.01	Dominant	+0.0002	-8.09	Dominant
Sensitivity colonoscopy[§]	+0.0002	-8.58	Dominant	+0.0001	-7.82	Dominant
Specificity colonoscopy[§]	+0.0002	-8.05	Dominant	+0.0002	-7.97	Dominant
Cost colonoscopy[§]	+0.0002	-4.18	Dominant	+0.0002	-11.56	Dominant
Cost polypectomy[§]	+0.0002	-8.03	Dominant	+0.0002	-7.65	Dominant
Complication rate of colonoscopy[§]	+0.0002	-7.93	Dominant	+0.0002	-8.09	Dominant
Cost treatment complications[§]	+0.0002	-7.99	Dominant	+0.0002	-8.51	Dominant
Cost treatment[§]	+0.0002	-8.05	Dominant	+0.0002	-7.96	Dominant

LE = life expectancy; ICER = incremental cost-effectiveness ratio; Dominant = the individualized strategy was both more effective and less costly than the uniform strategy.

* Lifetime per person cost for CRC screening and treatment after age 40y.

[†] For this assumption there was no high or low value. It was just varied from the base assumption where differences in CRC risk were caused by differences in adenoma incidence. In this sensitivity analysis, it was assumed that differences were caused by differences in progression rates of adenomas.

[‡] The incremental cost per life-year gained of the uniform 8-yearly colonoscopy strategy compared to the individualized strategy.

[§] Duration: low value = 10y, high value = 30y; Risk blacks: low value = 10% lower risk, high value = 10% higher risk than values in Table 6.1; Reach colonoscopy: low value = 80% reach cecum, high value = 99% reach cecum; Sensitivity colonoscopy: low and high values set at 95% CIs (see MISCAN-Colon microsimulation model in Materials and Methods section); Specificity colonoscopy: low value = 0.78, high value = 1; Cost colonoscopy: low value = $285, high value = $1012; Cost polypectomy: low value = $159, high value = $507; Complication rate of colonoscopy: low value = 1 per 1000, high value = 4 per 1000; Cost treatment complications: low value = $4360, high value = $26,000; Cost treatment: low and high values set at 95% CIs (see Table 6.2).

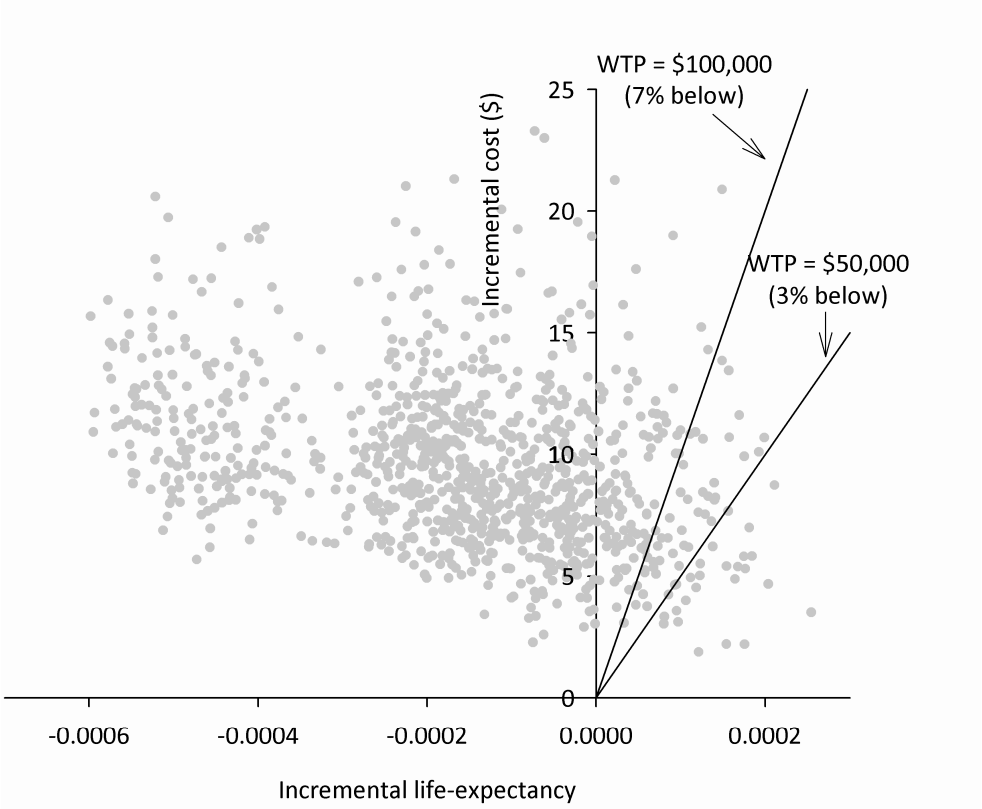

Figure 6.2: Multivariate uncertainty analysis by using 1000 simulations. This analysis simultaneously varies all parameters over the full range of possible values. Each point represents the incremental costs and life-years gained of uniform 8-yearly colonoscopy screening over individualized screening generated in one simulation; 83% of points fall in the upper left corner of the graph, which means that uniform screening is both less effective and more costly than individualized screening. The solid lines represent the willingness to pay (WTP) thresholds of $50,000 and $100,000. Points to the right and under this line represent simulations in which uniform screening was more effective than individualized screening at incremental costs of $50,000 or less and $100,000 or less, respectively

6.4 Discussion

The present analysis suggests that 8-yearly uniform and individualized colonoscopy recommendations by sex and race on a total population level are comparable in costs and effects: the overall (total population) benefit of individualization is limited (0.0002 additional life-years gained, $9.09 lower costs per person). This is explained by the fact that the black population constitutes no more than approximately 20% of the population. For blacks, the increase in life-years gained was more substantial (0.0078 life-years, approximately 14% of total life years saved with screening), which decreased the disparity in incidence and mortality compared to whites. Our results were robust for changes in model assumptions. In 1000 simulations with different model parameter

values, the 8-yearly uniform and individualized strategies remained equivalent in costs and effects. We found that, with individualizing screening, blacks are screened with a 1-year shorter interval than whites and start screening 6 years earlier, whereas the recommended screening ages and frequency for men and women remain similar.

Our findings support the recommendation of the American College of Gastroenterology to begin screening 5 years earlier for blacks than for whites. Starting screening at an earlier age, without increasing the number of screenings, results in saving 0.0052 additional life-years for blacks (data not shown). Also, increasing the number of screenings, as recommended from our study, significantly further increases the additional life years gained, to 0.0078. Individualization, therefore, can play a significant role in reducing disparities between blacks and whites. Our results are in line with other studies that showed that the average cost-effectiveness of CRC screening is better in black men than in other population subgroups.[249, 250] Based on these results, the investigators advocate earlier screening in blacks. However, basing individualized guidelines on average cost-effectiveness does not necessarily lead to efficient use of resources. In the present analysis, we determined individualized guidelines based on incremental cost-effectiveness and hence ensured efficient use of resources.[231, 232]

Besides the current recommendation of 4 screenings every 10 years from age 50 years to age 80 years, we also used another uniform colonoscopy strategy as a comparator to enable a fair comparison between uniform and individualized screening. We could not use the exact recommendation for that purpose, because it was not optimally cost-effective, although it was close. The current guidelines were not based on a formal decision analysis but on studies on colonoscopic efficiency[107] and on simplicity and clarity. Individualized guidelines are more complex than uniform ones, and, one, therefore, could argue that recommendations should not be individualized unless benefits are substantial. Individualized screening guidelines may confuse providers and consumers to the point of decreasing adherence. A decrease in adherence will easily offset the gains from individualization. Currently, 40% of black men and 32% of black women aged 50 years and older reported having had either a fecal occult blood test (FOBT) within the past year or a colorectal endoscopy within the past 5 years.[108] Based on these figures, much can be gained from increased adherence to screening guidelines. However, individualization of screening guidelines must be considered in the context of a general trend toward personalized medical care.[251, 252] As a result, screening adherence might improve, because individuals appreciate that the recommendation is based on their personal risk profile. In any case, in a situation in which individualization of medical care, and especially of screening, becomes the standard, it would be only natural to also account for race and sex differences, given the expected benefit and regardless of its size. To avoid too much complexity, one could recommend not changing the guidelines for whites but changing screening for blacks to every 9 years from age 45 years onward (a similar change as the results of this study). Compared to the current screening guidelines, this recommendation would result in 0.0076 more life-years gained for blacks, comparable with the 0.0078 found in this study.

In this analysis, we assumed that all disparities in cancer incidence are caused by differences in adenoma incidence. This assumption is supported by results from the Clinical Outcomes Research Initiative, which showed a higher percentage of patients with adenoma and with polyps >9 mm in blacks than in whites.[253] Furthermore, observational studies show that CRC risk factors have a similar effect on adenoma prevalence as on CRC incidence.[10, 11, 14, 15, 17, 18] Theoretically, a higher CRC

incidence could also be caused by more rapid adenoma and cancer progression. In this case, development of adenomas into CRC would have a shorter duration in blacks than in whites. When we assumed a faster progression for blacks, with a strongly reduced average preclinical disease duration, the benefit of individualization was slightly reduced.

We assumed that differences in the observed CRC incidence and stage distribution between blacks and whites reflect true differences in risk and are not because of differences in screening utilization. However, when considering that screening rates are lower for blacks than for whites,[108] the risk difference between blacks and whites may be smaller. The sensitivity analysis shows that, with a lower CRC risk in blacks (i.e., smaller difference with whites), the benefit of individualization was reduced. Furthermore, we only considered life-years gained and not quality-adjusted life-years. The reason for this is that the effect of CRC screening on quality of life has hardly been studied. There was 1 study that estimated 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.[254] However, quality of life at the moment of colonoscopy was not assessed. In population screening, large numbers of individuals undergo colonoscopy and even a minor effect of colonoscopy on quality of life will have a large impact on quality-adjusted life-years gained. Our results are only influenced by adjusting for quality of life when this differs between population subgroups. Crimmins[255] showed that blacks and whites not only differ in life expectancy (for which we accounted in the present analysis) but also in the proportion of healthy life-years, because blacks have more comorbidities at older ages. Therefore, intensive colonoscopy screening at older ages may be less feasible in blacks and also less beneficial in terms of quality-adjusted life-years gained, which reduces the potential benefit of individualization.

Age-specific CRC incidence and mortality in men reaches levels of risk comparable with women 4 to 8 years later in life.[256] Also, more women than men need to be screened for the detection of one advanced neoplasia.[189, 253, 257] Therefore, one may have expected that men need earlier and more intensive screening than women. However, our results show that the cost-effective individualized policies for men and women are comparable. This is because of the longer life expectancy of women. Although women have fewer advanced adenomas than men, more of those adenomas can evolve into CRC during the longer lifetime. This means that the number needed to screen to detect one advanced adenoma in women may be higher than in men but that the number of detected adenomas needed to prevent 1 case of CRC is lower. This makes the number needed to screen to prevent 1 CRC case, similar for men and women. Our finding of similar screening strategies is supported by the fact that the absolute number of CRC cases in men and women is comparable.[258]

This study aimed to explore the cost-effectiveness of individualization of screening guidelines. We restricted ourselves to colonoscopy, the preferred method of screening according to the American College of Gastroenterology.[259] Fortunately, the results can be generalized to other screening modalities. The costs per life-year gained will be different for other screening modalities, but the conclusion that individualization is cost-effective will remain, as well as the result that it is more cost-effective for blacks to be screened over a wider age range and with greater frequency than whites. We focused the analysis on black and white (including Hispanic) population subgroups. In a more extensive study, Hispanics and non-Hispanics could be considered separately, and Asians, Pacific Islanders, American Indians, and Native Alaskans could be included to explore further benefit of individualization. However, for these groups, incidence and mortality data will be based on small

numbers. CRC incidence and mortality tend to be lower in Hispanics, Asians, Pacific Islanders, American Indians, and Native Alaskans than in whites.[260] When these data are confirmed, a less intensive screening schedule for these groups could be considered.

In conclusion, our study suggests that 8-yearly uniform and individualized colonoscopy screening are comparable in costs and effects in the total population. However, individualized guidelines could contribute to decreasing disparities between blacks and whites. The acceptability and feasibility of individualized guidelines, therefore, should be explored.

Acknowledgement

We thank Martin Brown, PhD, and Robin Yabroff, PhD, of NCI for their assistance with obtaining cancer treatment costs by using SEER-Medicare data; John Allen, MD, and Joel Brill, MD, for their assistance in estimating costs of screening and complications; and William Larson, Marjorie Baldo, and Marilu Hu of the Centers for Medicaid and Medicare Services for providing cost data from the Centers for Medicaid and Medicare Services.

Appendix Table 1 to chapter 6, Total population (uniform): Efficient screening policies characterized by age range, screening interval, and number of scheduled examinations, and expressed as the 3% discounted lifetime costs and life expectancy of the policy

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs ($)*	Life expectancy at age 40
1	n.a.	70-70	1,701	22.4063
1	n.a.	65-65	1,720	22.4120
1	n.a.	64-64	1,725	22.4131
1	n.a.	63-63	1,731	22.4142
1	n.a.	62-62	1,737	22.4151
1	n.a.	61-61	1,747	22.4158
2	14	60-74	1,827	22.4213
2	14	59-73	1,845	22.4223
2	14	58-72	1,866	22.4233
3	9	57-75	2,010	22.4282
3	10	53-73	2,125	22.4315
3	9	53-71	2,151	22.4322
4	8	52-76	2,301	22.4353
4	8	51-75	2,349	22.4362
5	6	51-75	2,563	22.4390
5	7	47-75	2,733	22.4407
6	6	47-77	2,923	22.4426
7	5	48-78	3,077	22.4436
7	5	47-77	3,170	22.4441
8	5	47-82	3,223	22.4443
8	5	46-81	3,329	22.4448
8	5	43-78	3,659	22.4462
9	5	43-83	3,707	22.4464
10	5	43-88	3,732	22.4465
10	5	42-87	3,860	22.4466

n.a. = not applicable.

* Lifetime per person cost for CRC screening and treatment after age 40y.

AppendIx Table 2 to chapter 6, white men: Efficient screening policies characterized by age range, screening interval, and number of scheduled examinations, and expressed as the 3% discounted lifetime costs and life expectancy of the policy

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs ($)*	Life expectancy at age 40
1	n.a.	70-70	1,824	21.9125
1	n.a.	65-65	1,831	21.9186
1	n.a.	63-63	1,836	21.9211
1	n.a.	62-62	1,840	21.9221
1	n.a.	61-61	1,848	21.9229
2	14	60-74	1,916	21.9276
2	14	59-73	1,933	21.9288
2	14	58-72	1,953	21.9297
3	9	57-75	2,082	21.9343
3	8	57-73	2,104	21.9350
3	8	56-72	2,141	21.9360
3	9	53-71	2,220	21.9383
4	7	53-74	2,361	21.9412
4	7	52-73	2,413	21.9421
5	6	51-75	2,609	21.9445
6	6	47-77	2,962	21.9478
7	5	48-78	3,103	21.9488
8	5	47-82	3,241	21.9493
8	5	43-78	3,684	21.9511
9	5	43-83	3,723	21.9512
10	5	43-88	3,742	21.9513
10	5	42-87	3,871	21.9513

n.a. = not applicable.

* Lifetime per person cost for CRC screening and treatment after age 40y

Appendix Table 3 to chapter 6, black men: Efficient screening policies characterized by age range, screening interval, and number of scheduled examinations, and expressed as the 3% discounted lifetime costs and life expectancy of the policy

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs ($)*	Life expectancy at age 40
1	n.a.	64-64	1,746	19.8487
1	n.a.	63-63	1,750	19.8503
1	n.a.	62-62	1,754	19.8519
1	n.a.	61-61	1,760	19.8533
1	n.a.	60-60	1,767	19.8546
1	n.a.	59-59	1,777	19.8558
2	15	58-73	1,840	19.8612
2	14	58-72	1,846	19.8616
2	14	57-71	1,866	19.8629
3	11	53-75	2,035	19.8721
3	10	53-73	2,056	19.8731
3	10	52-72	2,090	19.8745
3	9	52-70	2,116	19.8754
4	9	48-75	2,342	19.8822
4	8	48-72	2,401	19.8834
5	7	47-75	2,582	19.8871
5	7	46-74	2,652	19.8882
6	6	47-77	2,735	19.8894
6	6	46-76	2,817	19.8904
6	6	45-75	2,906	19.8913
7	5	44-74	3,249	19.8945
8	5	43-78	3,402	19.8956
8	5	42-77	3,527	19.8961
9	5	42-82	3,556	19.8962
10	5	42-87	3,570	19.8962

n.a. = not applicable.

* Lifetime per person cost for CRC screening and treatment after age 40y.

Appendix Table 4 to chapter 6, white women: Efficient screening policies characterized by age range, screening interval, and number of scheduled examinations, and expressed as the 3% discounted lifetime costs and life expectancy of the policy

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs ($)*	Life expectancy at age 40
1	n.a.	72-72	1,563	23.4026
1	n.a.	71-71	1,567	23.4035
1	n.a.	70-70	1,573	23.4045
1	n.a.	65-65	1,606	23.4091
1	n.a.	64-64	1,614	23.4099
1	n.a.	63-63	1,624	23.4106
2	14	61-75	1,721	23.4167
2	14	60-74	1,742	23.4177
2	14	59-73	1,762	23.4185
2	14	58-72	1,785	23.4192
3	9	57-75	1,950	23.4242
3	10	53-73	2,069	23.4265
4	8	53-77	2,221	23.4293
4	8	52-76	2,267	23.4301
4	8	51-75	2,314	23.4309
5	7	51-79	2,458	23.4326
5	6	51-75	2,551	23.4336
6	6	47-77	2,925	23.4365
7	6	46-82	3,074	23.4374
8	5	46-81	3,363	23.4387
9	5	44-84	3,634	23.4396
9	5	43-83	3,750	23.4399
10	5	43-88	3,785	23.4399
10	5	42-87	3,911	23.4400

n.a. = not applicable.

* Lifetime per person cost for CRC screening and treatment after age 40y.

Appendix Table 5 to chapter 6, black women: Efficient screening policies characterized by age range, screening interval, and number of scheduled examinations, and expressed as the 3% discounted lifetime costs and life expectancy of the policy

Policy			Resources and benefits	
No. of scheduled exams	Interval between exams (years)	Age range	Costs ($)*	Life expectancy at age 40
1	n.a.	63-63	1,716	21.9029
1	n.a.	62-62	1,721	21.9045
1	n.a.	61-61	1,729	21.9059
1	n.a.	60-60	1,736	21.9071
1	n.a.	59-59	1,748	21.9081
2	15	59-74	1,819	21.9139
2	14	58-72	1,842	21.9157
2	15	57-72	1,857	21.9167
2	14	57-71	1,865	21.9171
3	11	53-75	2,060	21.9277
3	10	52-72	2,117	21.9307
4	8	51-75	2,299	21.9359
4	8	49-73	2,403	21.9385
5	7	47-75	2,671	21.9435
6	6	47-77	2,851	21.9464
6	6	46-76	2,934	21.9475
8	5	43-78	3,567	21.9525
9	5	43-83	3,613	21.9527
9	5	42-82	3,737	21.9530
10	5	42-87	3,765	21.9530

n.a. = not applicable.

* Lifetime per person cost for CRC screening and treatment after age 40y.

Chapter 7: Evaluating test strategies for colorectal cancer screening: A decision analysis for the U.S. Preventive Services Task Force

Abstract

Background: The U.S. Preventive Services Task Force requested a decision analysis to inform their update of recommendations for colorectal cancer screening

Objectives: To assess life-years gained and colonoscopy requirements for colorectal cancer screening strategies and identify a set of recommendable screening strategies.

Design: Decision analysis using 2 colorectal cancer microsimulation models from the Cancer Intervention and Surveillance Modeling Network.

Data sources: Derived from the literature.

Target population: U.S. average-risk 40-year-old population

Perspective: Societal

Time horizon: Lifetime

Interventions: Fecal occult blood tests (FOBTs), flexible sigmoidoscopy, or colonoscopy screening beginning at age 40, 50, or 60 years and stopping at age 75 or 85 years, with screening intervals of 1, 2, or 3 years for FOBT and 5, 10, or 20 years for sigmoidoscopy and colonoscopy.

Outcome measures: Number of life-years gained compared to no screening and number of colonoscopies and non-colonoscopy tests required.

Results of base-case analysis: Beginning screening at age 50 years was consistently better than at age 60. Decreasing the stop age from 85 to 75 years decreased life-years gained by 1% to 4%, whereas colonoscopy use decreased by 4% to 15%. Assuming equally high adherence, 4 strategies provided similar life-years gained: colonoscopy every 10 years, annual Hemoccult SENSA (Beckman Coulter, Fullerton, California) testing or fecal immunochemical testing, and sigmoidoscopy every 5 years with mid-interval Hemoccult SENSA testing. Annual Hemoccult II and flexible sigmoidoscopy every 5 years alone were less effective.

Results of sensitivity analysis: The results were most sensitive to beginning screening at age 40 years.

Limitation: The stop age for screening was based only on chronologic age.

Conclusion: The findings support colorectal cancer screening with the following: colonoscopy every 10 years, annual screening with a sensitive FOBT, or flexible sigmoidoscopy every 5 years with a mid-interval sensitive FOBT from age 50 to 75 years.

7.1 Introduction

Despite recent declines in both incidence and mortality,[261] colorectal cancer remains the second most common cause of death from cancer in the United States.[262] Screening for colorectal cancer reduces mortality by allowing physicians to detect cancer at earlier, more treatable stages, as well as to identify and remove adenomatous polyps (asymptomatic benign precursor lesions that may lead to colorectal cancer). Many tests are available for screening, such as fecal occult blood tests (FOBTs), flexible sigmoidoscopy, and colonoscopy. Screening with FOBT (Hemoccult II, Beckman Coulter, Fullerton, California) has been shown to reduce colorectal cancer mortality by 15% to 33% in randomized, controlled trials,[28, 29, 85] and screening with more sensitive FOBTs, flexible sigmoidoscopy, colonoscopy, or combinations of these tests may reduce the burden of colorectal cancer even more.[26, 107] In the absence of adequate clinical trial data on several recommended screening strategies, microsimulation modeling can provide guidance on the risks, benefits, and testing resources required for different screening strategies to reduce the burden of colorectal cancer.

In July 2002, the U.S. Preventive Services Task Force (USPSTF) concluded that there was sufficient evidence to recommend strongly that all average-risk adults 50 years of age or older should be offered colorectal cancer screening.[263] However, the logistics of screening, such as the type of screening test, screening interval, and age at which to stop screening, were not evaluated in terms of the balance of benefits and potential harms. The USPSTF has again addressed recommendations for colorectal cancer screening with a systematic review of the evidence[264] on screening tests. For this assessment, the USPSTF requested a decision analysis to project expected outcomes of various strategies for colorectal cancer screening. Two independent microsimulation modeling groups from the Cancer Intervention and Surveillance Modeling Network (CISNET), funded by the U.S. National Cancer Institute, used a comparative modeling approach to compare life-years gained relative to resource use of different strategies for colorectal cancer screening.

7.2 Methods

We used 2 microsimulation models, MISCAN (Microsimulation Screening Analysis)[76, 77, 185] and SimCRC (Simulation Model of Colorectal Cancer),[241] to estimate the life-years gained relative to no screening and the colonoscopies required (that is, an indicator for resource use and risk for complications) for different colorectal cancer screening strategies defined by test, age at which to begin screening, age at which to stop screening, and screening interval. We aimed to identify a set of recommendable strategies with similar clinical benefit and an efficient use of colonoscopy resources. Using 2 models (that is, a comparative modeling approach) adds credibility to the results and serves as a sensitivity analysis on the underlying structural assumptions of the models, particularly pertaining to the unobservable natural history of colorectal cancer.

Microsimulation models

Standardized model profiles are available at http://cisnet.cancer.gov/profiles/. In brief, both models simulate the life histories of a large population of individuals from birth to death. As each individual

ages, there is a chance that an adenoma will develop. One or more adenomas can occur in an individual, and each adenoma can independently develop into preclinical (that is, undiagnosed) colorectal cancer (Figure 1.8). The risk for developing an adenoma depends on age, sex, and baseline individual risk. The models track the location and size of each adenoma; these characteristics influence disease progression and the chance that the adenoma will be found by screening. The size of adenomas can progress from small (1-5 mm) to medium (6-9 mm) to large (≥ 10 mm). Some adenomas eventually become malignant, transforming to stage I preclinical cancer. Preclinical cancer has a chance of progressing through stages I to IV and may be diagnosed by symptoms at any stage. Survivorship after diagnosis depends on the stage of disease.

The natural history component of each model was calibrated to 1975-1979 clinical incidence data[135] and adenoma prevalence from autopsy studies in the same period.[174-183] We used this period because incidence rates and adenoma prevalence had not yet been affected by screening. We corrected the adenoma prevalence for studies of non-U.S. populations by using standardized colorectal cancer incidence ratios. The models use all-cause mortality estimates from the U.S. life tables and stage-specific data on colorectal cancer survival from the 1996-1999 Surveillance, Epidemiology, and End Results program.[135] Table 7.1 compares outcomes from the natural history components of the models.

The effectiveness of a screening strategy is modeled through a test's ability to detect lesions (that is, adenomas or preclinical cancer). Once screening is introduced, a simulated person who has an underlying lesion has a chance of having it detected during a screening round depending on the sensitivity of the test for that lesion and whether the lesion is within the reach of the test. Screened persons without an underlying lesion can have a false-positive test result and undergo unnecessary follow-up colonoscopy. Hyperplastic polyps are not modeled explicitly, but their detection is reflected in the specificity of the screening tests. The models incorporate the risk for fatal complications associated with perforation during colonoscopy. Both models have been validated against the long-term reductions in incidence and mortality of colorectal cancer with annual FOBT reported in the Minnesota Colon Cancer Control Study[31, 85, 265] and show good concordance with the trial results.

Table 7.1: Comparison of the natural history outcomes from the Microsimulation Screening Analysis (MISCAN) and Simulation Model of Colorectal Cancer (SimCRC) models

	MISCAN by age, %*			SimCRC by age, %*		
Outcome	40y	50y	60y	40y	50y	60y
Adenoma prevalence	10.9	28.7	36.7	10.2	18.3	29.5
Size distribution of adenomas						
1-5 mm	60.9	64.8	52.6	59.3	53.9	51.1
6-9 mm	20.9	19.0	25.3	31.6	34.4	35.8
≥10 mm	18.2	16.2	22.1	9.1	11.7	13.0
Location of adenomas						
Proximal	34.3	34.3	34.3	62.0	62.4	62.8
Distal	34.5	34.5	34.5	30.5	30.4	30.3
Rectum	31.2	31.2	31.2	7.5	7.2	6.8
Cumulative CRC incidence						
10y	0.2	0.7	1.6	0.2	0.7	1.4
20y	0.9	2.3	4.0	0.9	2.1	3.4
Lifetime	7.3	7.1	6.4	6.2	5.9	5.3
Stage distribution of CRC cases						
Stage I	16.6	21.1	19.3	24.0	21.9	19.4
Stage II	23.0	28.3	31.4	39.6	35.1	34.8
Stage III	33.7	26.3	26.1	20.0	22.2	22.6
Stage IV	26.7	24.4	23.2	16.4	20.7	23.2

CRC = colorectal cancer.

* Because of rounding, not all percentages add to 100%.

Strategies for colorectal cancer screening

In consultation with the USPSTF, we included the following basic strategies: 1) no screening, 2) colonoscopy, 3) FOBT (Hemoccult II, Hemoccult SENSA [Beckman Coulter], or fecal immunochemical testing), 4) flexible sigmoidoscopy (with biopsy), and 5) flexible sigmoidoscopy combined with Hemoccult SENSA. For each basic strategy, we evaluated start ages of 40, 50, and 60 years and stop ages of 75 and 85 years. For the FOBT strategies, we considered screening intervals of 1, 2, and 3 years, and for the sigmoidoscopy and colonoscopy strategies, we considered intervals of 5, 10, and 20 years. These variations resulted in 145 strategies: 90 single-test strategies, 54 combination-test strategies, and 1 no-screening strategy. The stop age reflects the oldest possible age at which to screen, but the actual stopping age is dictated by the start age and screening interval.

In the base-case, we assumed 100% adherence for screening tests, follow-up of positive findings, and surveillance of persons found to have adenomas. Individuals with a positive FOBT result or with an adenoma detected by sigmoidoscopy were referred for follow-up colonoscopy. For years in which both tests were due for the combined strategy, the FOBT was performed first; if the result was positive, the patient was referred for follow-up colonoscopy. In those years, flexible sigmoidoscopy was done only for patients with a negative FOBT result. If findings on follow-up colonoscopy were negative, the individual was assumed to undergo subsequent screening with colonoscopy with a 10-year interval (as long as results of the repeated colonoscopy were negative) and did not return to the initial screening schedule, as is the recommendation of the U.S. Multi-Society Task Force and American Cancer Society.[71, 107] All individuals with an adenoma detected were followed with colonoscopy surveillance per the Multi-Society guidelines.[71, 192] The surveillance interval depended on the number and size of the adenomas detected on the last colonoscopy; it ranged from 3 to 5 years and was assumed to continue for the remainder of the person's lifetime.

We estimated the test characteristics of colorectal cancer screening from a review of the available literature (Table 7.2).[42] We conducted this review independently of and parallel in time with the systematic evidence review performed for the USPSTF.[264]

Table 7.2: Test characteristics used in the Microsimulation Screening Analysis and Simulation Model of Colorectal Cancer models[42]

Test characteristic	Base-case value	Sensitivity analysis	
		Best-case value	Worst-case value
Hemoccult II			
Specificity, %	98.0	99.0	95.0
Sensitivity for adenomas 1-5 mm, %*	2.0	1.0	5.0
Sensitivity for adenomas 6-9 mm, %	5.0	13.7	5.0
Sensitivity for adenomas ≥10 mm, %	12.0	27.5	8.9
Sensitivity for cancer, %	40.0	50.0	25.0
Reach	Whole colorectum	Not varied	Not varied
Mortality rate	0	Not varied	Not varied
Hemoccult SENSA			
Specificity, %	92.5	95.0	90.0
Sensitivity for adenomas 1-5 mm, %*	7.5	5.0	10.0
Sensitivity for adenomas 6-9 mm, %	12.4	26.2	10.0
Sensitivity for adenomas ≥10 mm, %	23.9	49.4	17.7
Sensitivity for cancer, %	70.0	87.0	50.0
Reach	Whole colorectum	Not varied	Not varied
Mortality rate	0	Not varied	Not varied
Fecal immunochemical test			
Specificity, %	95.0	98.0	92.5
Sensitivity for adenomas 1-5 mm, %*	5.0	2.0	7.5
Sensitivity for adenomas 6-9 mm, %	10.1	24.0	7.5
Sensitivity for adenomas ≥10 mm, %	22.0	48.0	16.0
Sensitivity for cancer, %	70.0	87.0	50.0
Reach	Whole colorectum	Not varied	Not varied
Mortality rate	0	Not varied	Not varied

Table 7.2 continued

Test characteristic	Base-case value	Sensitivity analysis	
		Best-case value	Worst-case value
Sigmoidoscopy (within reach)			
Specificity, %	92.0	Not varied	Not varied
Sensitivity for adenomas 1-5 mm, %	75.0	79.0	70.0
Sensitivity for adenomas 6-9 mm, %	85.0	92.0	80.0
Sensitivity for adenomas ≥10 mm, %	95.0	99.0	92.0
Sensitivity for cancer, %	95.0	99.0	92.0
Reach[†]	80% to sigmoid-descending junction, 40% to splenic flexure	100% to sigmoid-descending junction, 80% to splenic flexure	60% to sigmoid-descending junction, 30% to splenic flexure
Mortality rate	0	Not varied	Not varied
Colonoscopy (within reach)			
Specificity, %	90.0	Not varied	Not varied
Sensitivity for adenomas 1-5 mm, %	75.0	79.0	70.0
Sensitivity for adenomas 6-9 mm, %	85.0	92.0	80.0
Sensitivity for adenomas ≥10 mm, %	95.0	99.0	92.0
Sensitivity for cancer, %	95.0	99.0	92.0
Reach	95% to end of cecum, remaining 5% between rectum and cecum	Not varied	Not varied
Mortality rate	1 per 10,000	Not varied	Not varied

* We assume that small adenomas do not bleed and cannot be detected by fecal occult blood tests (FOBTs). The sensitivity of FOBTs for adenomas 1-5 mm is based on the false-positive rate (that is, 1 - specificity).

[†] The sensitivity of sigmoidoscopy for colorectal cancer over the whole colorectum is 72% with the Microsimulation Screening Analysis model and 61% with the Simulation Model of Colorectal Cancer.

Evaluation of outcomes

Determination of efficient strategies

The most effective strategy was defined as the one with the greatest life-years gained relative to no screening. However, it is important to consider the relative intensity of test use required to achieve those gains. The more effective strategies tended to be associated with more colonoscopies on average in a person's lifetime, which translated into an increased risk for colonoscopy-related complications. We used an approach that mirrors that of cost-effectiveness analysis[266] to identify the set of efficient, or dominant, strategies within each test category. A strategy was considered dominant when no other strategy or combination of strategies provided more life-years with the same number of colonoscopies. We conducted this analysis separately for each of the 5 basic screening strategies because the number of non-colonoscopy tests differed by strategy. We then ranked the efficient screening strategies by increasing effectiveness and calculated the incremental number of colonoscopies (ДCOL) per 1000, the incremental life-years gained (ДLYG) per 1000, and the incremental number of colonoscopies necessary to achieve 1 year of life (ДCOL/ДLYG) relative to the next less effective strategy, which we call the "efficiency ratio". The line connecting the set of efficient strategies is called the "efficient frontier". We also identified "near-efficient" strategies—strategies that yielded life-years gained within 98% of the efficient frontier.

Determination of recommendable strategies at a certain level of effectiveness

We further considered only efficient or near-efficient strategies. We assumed that the set of recommendable strategies would have the same start and stop age because recommending different start and stop ages by test may be confusing for patients and practitioners. We looked at the incremental number of colonoscopies relative to the life years gained to determine what would be reasonable start and stop ages. For a given start and stop age, we selected a colonoscopy strategy; the default was the generally recommended 10-year screening interval. From the other test categories, we selected strategies with a screening effectiveness most similar to that of colonoscopy and a lower efficiency ratio than that for colonoscopy. This was because strategies with more intensive use of tests other than colonoscopy should have a lower efficiency ratio than strategies with less intensive (or no) use of non-colonoscopy tests (that is, this ratio would be higher if other tests were included in the numerator). Alternative sets of recommendable strategies for colorectal cancer screening were obtained with different colonoscopy strategies selected as the initial comparator.

Sensitivity analyses

The primary sensitivity analysis was the comparison of findings across the 2 independently developed microsimulation models. We also performed sensitivity analyses on test characteristics in which we used all of the least favorable values in a worst-case analysis and all of the most favorable values in a best-case analysis (Table 7.2). For colonoscopy and sigmoidoscopy, we used the confidence intervals reported in the meta-analysis by van Rijn and colleagues[53] as the range tested. For FOBT, we used the

ranges reported in the literature.[42, 264] To assess the relative effect of decreased adherence, we explored the impact of overall adherence rates of 50% and 80%. We incorporated correlation of screening behavior within an individual by assuming that the population comprises 4 groups: those who are never screened and those with low, moderate, and high adherence; 10% of the population was in the never-screened group and 30% were in each of the other groups. For both overall screening adherence assumptions (that is, 50% and 80%), we assumed that adherence with follow-up and surveillance was 75%, 85%, and 95% for those with low, moderate, and high adherence, respectively. We assumed that individuals remain in their screening behavior group.

Role of the funding source

The National Cancer Institute supported the infrastructure for the CISNET models. The Agency for Healthcare Research and Quality funded this work and provided project oversight and review. The authors worked with 4 USPSTF members to specify the overall questions, select the strategies, and resolve methodological issues during the conduct of the review. The draft decision analysis was reviewed by 3 external peer reviewers (listed in the acknowledgments) and was revised for the final version. The authors have sole responsibility for the models and model results. This research did not include patient-specific information and was exempt from institutional review board review.

7.3 Results

Table 7.3 presents life-years gained, the number of colonoscopies, and the efficiency ratio for each efficient and near-efficient colonoscopy strategy for both models. Similar results for the other tests can be found in the Appendix Tables to this chapter. For illustration, Figure 7.1 presents the life-years gained relative to the number of colonoscopies and the efficient frontier for all colonoscopy strategies.

Table 7.3: Efficient and near-efficient strategies for colonoscopy screening

	Outcomes per 1000 persons				
Test, Age Begin - Age Stop, Interval*	COL	LYG	ДCOL	ДLYG	ДCOL/ДLYG
MISCAN					
COL, 60-75, 20	2,175	156	-	-	-
COL, 50-75, 20	3,325	203	1,150	47	24.7
COL, 50-75, 10	**4,136**	**230**	**811**	**27**	**29.6**
COL, 50-85, 10	4,534	236	398	5	72.9
COL, 50-75, 5	5,895	254	1,362	18	74.8
COL, 50-85, 5	6,460	257	565	4	156.1
SimCRC					
COL, 60-75, 20	1,780	165	-	-	-
COL, 50-75, 20	2,885	246	1,106	82	13.5
COL, 50-75, 10	**3,756**	**271**	**871**	**25**	**34.7**
COL, 50-85, 10	4,114	273	358	2	Near-efficient[†]
COL, 50-75, 5	5,572	282	1,816	10	178.8
COL, 50-85, 5	6,031	282	459	1	975.7

COL = colonoscopy; ДCOL = incremental number of colonoscopies compared to the next-best non-dominated strategy; LYG = life-years gained compared to no screening; ДLYG = incremental number of life-years gained compared to the next-best non-dominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.

* Bold indicates recommendable strategy. Age and intervals expressed as years.

[†] Strategy yields life-years gained within 98% of the efficient frontier.

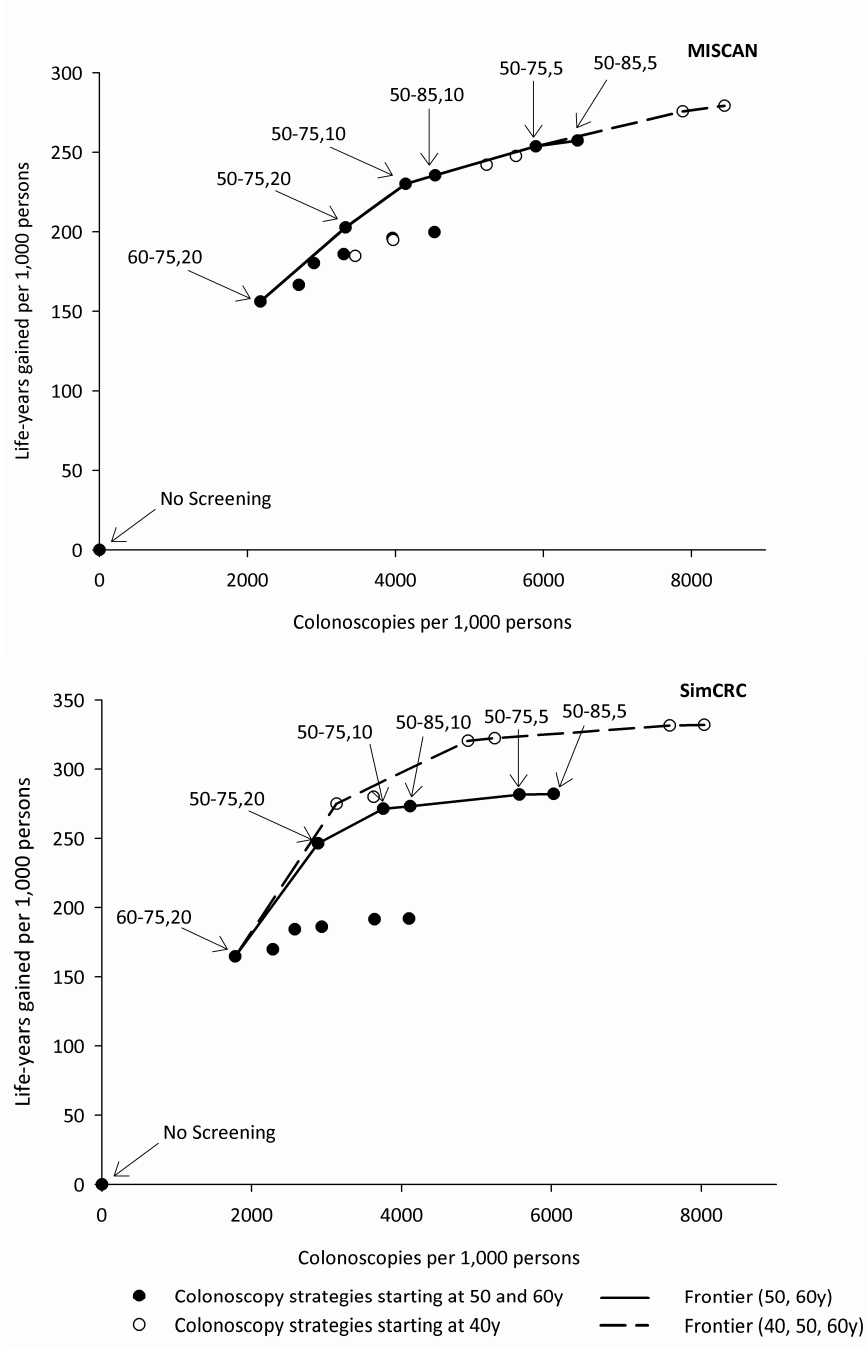

Figure 7.1: Colonoscopies and life-years gained (compared to no screening) for a cohort of 1000 forty-year-olds for 18 colonoscopy screening strategies that vary by start age, stop age, and screening interval. The numbers represent the following: age to begin-age to stop screening, interval. MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.

Age at which to begin screening

The results from the MISCAN and SimCRC models were consistent in evaluating strategies with age to begin screening of 50 or 60 years, with the start age of 50 predominating among the efficient or near-efficient strategies (Table 7.3 and Appendix Tables to this chapter). However, the SimCRC model showed favorable results for the strategies in which screening begins at age 40 years, but these results were not corroborated by the MISCAN model. To illustrate this difference, Figure 7.1 shows the efficient frontier with age 40 included for colonoscopy ("Frontier 40, 50, 60y") and without age 40 ("Frontier 50, 60y"). Similar results were found for the other tests (see the technical report available at www.ahrq.gov). Because the evidence for both adenoma prevalence at age 40 and the duration of the adenoma-carcinoma sequence is weak, we restricted further analysis to start ages of 50 and 60.

Age at which to stop screening

For both models and all tests, decreasing the stop age from 85 to 75 yielded small reductions in life-years gained relative to large reductions in the number of colonoscopies required (Appendix Tables to this chapter). For example, stopping screening at age 75 years instead of 85 years for colonoscopy every 10 years would decrease the number of life-years gained with colonoscopy screening by 5 per 1000 individuals for MISCAN and by 2 per 1000 individuals for SimCRC, but would substantially decrease the number of colonoscopies by 398 and 358 per 1000 individuals for MISCAN and SimCRC, respectively (Table 7.3). This is illustrated by the substantial reduction in the efficiency ratio for these 2 strategies, from 73 to 30 for MISCAN and 179 to 35 for SimCRC.

Screening interval

In general, strategies with longer intervals provided fewer life-years gained than did strategies with shorter intervals. For all single test strategies, the currently recommended intervals of annual FOBT, flexible sigmoidoscopy every 5 years, and colonoscopy every 10 years provided a reasonable ratio of incremental colonoscopies per life-year gained (8 -35) for ages 50 to 75 years (Appendix Tables to this chapter). The results from both models showed that the current recommendation for the combination of flexible sigmoidoscopy every 5 years with a high-sensitivity FOBT annually had a high efficiency ratio, and that moving to a strategy of sigmoidoscopy every 5 years with FOBT every 3 years would minimally decrease the number of life-years gained with combination screening (by 9 per 1000 individuals for MISCAN and by 17 per 1000 individuals for SimCRC) and would substantially decrease the number of colonoscopies (by 765 per 1000 individuals for MISCAN and by 1011 per 1000 individuals for SimCRC for ages 50 to 75 years) (Appendix Tables to this chapter). This would substantially reduce the incremental colonoscopies required for an additional life-year gained from 140 to 16 for MISCAN and from 76 to 7 for SimCRC.

Identifying a set of recommendable strategies for colorectal cancer screening

In the preceding analysis, we found that a start age of 50 years and a stop age of 75 years were most reasonable when we considered both benefit and resource use. For those start and stop ages, we first selected the colonoscopy strategy with 10-year intervals because this has been the recommended interval; shortening the interval resulted in a marked increase in efficiency ratio (from 30 to 75 for MISCAN and 35 to 179 for SimCRC) (Table 7.3). The non-colonoscopy strategies were then chosen to have the same start and stop ages and a lower efficiency ratio, while saving similar life-years as that for colonoscopy (Table 7.4).

Table 7.4: Outcomes for the recommendable set of efficient screening strategies

Test, Age Begin - Age Stop, Interval*	Outcomes per 1000 persons					
	COL	Non-COL Tests	LYG	Efficiency ratio†	Incidence reduction, %	Mortality reduction, %
MISCAN						
COL, 50-75, 10	4,136	0	230	29.6	51.9	64.6
Hemoccult SENSA, 50-75, 1	3,350	9,541	230	30.9	49.7	66.0
FIT, 50-75, 1	2,949	11,773	227	25.9	47.2	64.6
Hemoccult II, 50-75, 1	1,982	16,231	194	14.3	37.1	55.3
FSIG, 50-75, 5	1,911	4,139	203	9.7	46.8	58.5
FSIG + SENSA, 50-75, 5, 3	2,870	7,685	230	16.3	51.2	65.7
SimCRC						
COL, 50-75, 10	3,756	0	271	34.7	80.6	84.4
Hemoccult SENSA, 50-75, 1	2,654	9,573	259	22.9	73.2	81.2
FIT, 50-75, 1	2,295	11,830	256	19.7	70.8	80.0
Hemoccult II, 50-75, 1	1,456	16,239	218	9.6	56.6	69.0
FSIG, 50-75, 5	995	4,483	199	8.4	59.0	62.2
FSIG + SENSA, 50-75, 5, 3	1,655	11,623	257	7.0	72.2	79.3

COL = colonoscopy; FIT = fecal immunochemical test; FSIG = flexible sigmoidoscopy; LYG = life-years gained compared to no screening; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.

* Age and intervals expressed as years.

† Efficiency ratio corresponds with ΔCOL/ΔLYG in the Appendix Tables to this chapter and represents the relative burden per unit of benefit achieved.

The sensitive annual FOBT strategies (Hemoccult SENSA and fecal immunochemical test) were similar to colonoscopy every 10 years in terms of life-years gained. The less sensitive FOBT (Hemoccult II) performed annually did not have effectiveness similar to that of the other FOBTs or to that of colonoscopy. Flexible sigmoidoscopy every 5 years, although showing a reasonable efficiency ratio, did not have effectiveness similar to that of the other strategies. The combination of flexible sigmoidoscopy every 5 years with Hemoccult SENSA every 3 years had a reasonable efficiency ratio (lower than that of colonoscopy and the sensitive FOBTs) and had relatively similar life-years gained. Had we selected the 20-year interval for colonoscopy as the comparator strategy instead of the 10-year interval, the set of strategies would include biennial screening for sensitive FOBT, annual screening for Hemoccult II, and screening with sigmoidoscopy every 10 years in combination with FOBT every 3 years. The life-years gained for this set of screening strategies is approximately 8% to 12% lower than that shown in Table 7.4.

Sensitivity analysis

Our overall conclusions did not change with variations in test characteristics. As expected, results for the worst-case analysis showed fewer life-years gained than results for the base-case, and the best-case analysis had more life-years gained. For strategies that remained on the efficient frontier, the incremental number of colonoscopies per life-year gained was typically greater than the base-case value with the best-case assumption and lower with the worst-case assumption.

Figure 7.2 shows the expected number of colonoscopies and life-years gained for adherence of 50%, 80%, and 100% for the recommended strategies shown in Table 7.4. When adherence was relatively high at 80%, the colonoscopy strategy (that is, screening every 10 years from ages 50 to 75) was the most effective in term of life-years gained; Hemoccult SENSA, fecal immunochemical testing, and the combination strategies all provided life-years gained within 8% of those of the colonoscopy strategy. When overall adherence was only 50%, the colonoscopy strategy was no longer the most effective, and Hemoccult SENSA, fecal immunochemical testing, and the combination strategies had life-years gained greater than or equivalent to those of the colonoscopy strategy. Annual Hemoccult II and flexible sigmoidoscopy every 5 years remained the least attractive alternatives in terms of life-years gained across different adherence levels.

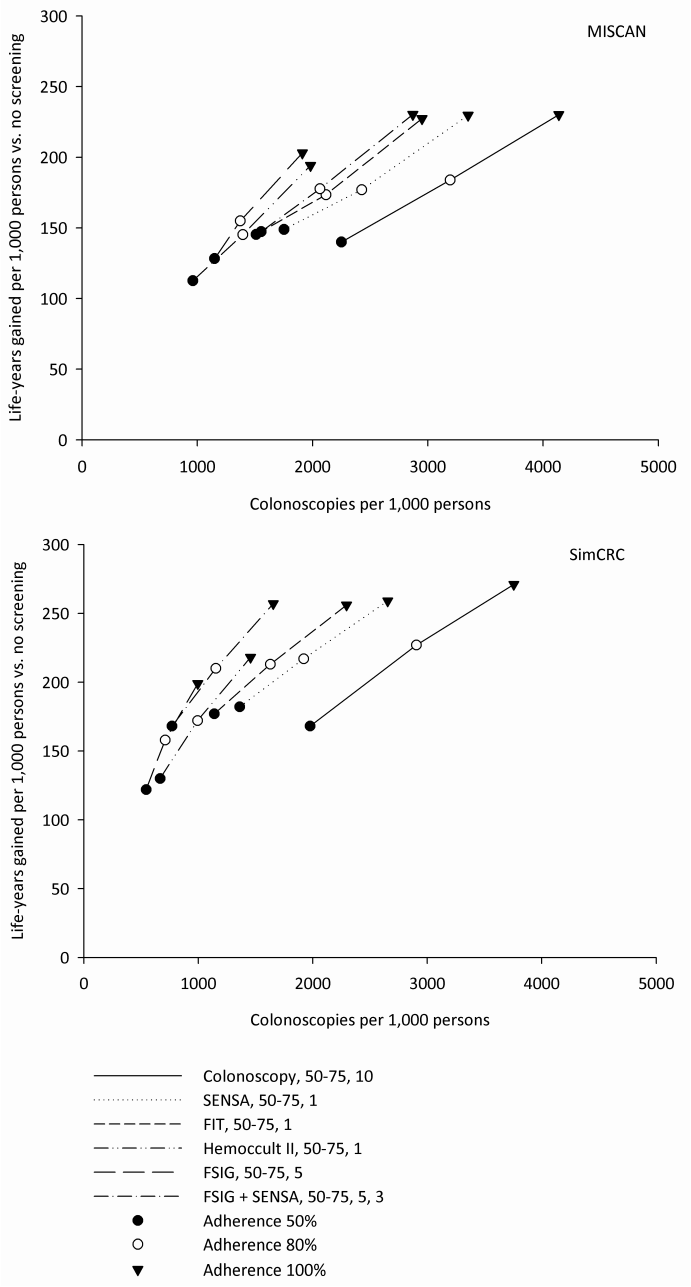

Figure 7.2: Colonoscopies and life-years gained, by adherence level for the recommendable set of screening strategies. SENSA = Hemoccult SENSA; FIT = fecal immunochemical testing; FSIG = flexible sigmoidoscopy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.
The numbers after the test name represent the following: age to begin-age to stop screening, interval.

7.4 Discussion

We used 2 independent microsimulation models to evaluate different strategies for colorectal cancer screening defined by screening test, age at which to begin screening, interval to repeat screening, and age at which to stop screening. Our goal was to provide the USPSTF with information that synthesizes and translates multiple sources of data, such as screening test characteristics, into projections of clinical benefit and resource utilization for multiple screening options. We found several screening strategies (colonoscopy every 10 years, high-sensitivity FOBT performed annually, and flexible sigmoidoscopy every 5 years with Hemoccult SENSA every 2 to 3 years) that provide similar gains in life-years if there is equally high adherence for all aspects of the screening process. Our analysis also found that annual FOBT with a lower-sensitivity test (for example, Hemoccult II) and flexible sigmoidoscopy alone resulted in fewer life-years gained relative to other strategies. Our analysis confirmed the current recommendation to begin screening at age 50 years in an asymptomatic general population and showed that stopping at age 75 years after consecutive negative screenings since age 50 years provides almost the same benefit as stopping at age 85 years, but with substantially fewer colonoscopy resources and risk for complications.

Our decision analysis represents the first time that the USPSTF has included simulation modeling to help inform their decision on recommendations. The USPSTF had previously recommended screening for all asymptomatic persons beginning at age 50 years but did not recommend one test over another or an age at which to stop screening.[263] Although randomized, controlled trials are the preferred method for establishing effectiveness of (screening) interventions, they are expensive, require long follow-up, and can address only a limited number of comparison groups. However, well-validated microsimulation models may be used to highlight the tradeoff between clinical benefit and resource utilization from different screening policies and inform decision making with standardized comparisons of net benefits and risks. The process with which our analysis was conducted represents an important advancement from evidence-based to evidence-informed medicine, and the use of more than 1 model, as advocated by CISNET, adds credibility when model results agree.

We found that colorectal cancer screening with high sensitivity FOBT (Hemoccult SENSA or fecal immunochemical test) provided similar life-years gained as colonoscopy, even though the individual test characteristics were substantially better for colonoscopy (Table 7.2). This finding was partially due to the fact the FOBT must be performed every year compared to every 10 years for colonoscopy, and the test characteristics are assumed to remain unchanged with each subsequent screening. For example, if an adenoma was missed by a screening test in one cycle, then the chance that it would be missed again on the next examination is still based on the false-negative rate (1 - sensitivity for adenomas). There is little evidence on whether test sensitivity varies with increasing rounds of testing. In addition, a substantial percentage of individuals receiving annual FOBT screening will eventually have a false-positive screening result with referral for colonoscopy. Once confirmed to be negative by colonoscopy, they then have colonoscopy screening every 10 years, as per guidelines. For example, with a specificity of 92.5% for Hemoccult SENSA, the percentage of people in a colonoscopy screening program is about 54% after 10 FOBTs and about 79% after 20 FOBTs.

There has been no recommended stop age for colorectal cancer screening.[71, 107, 263] However, our results indicate that continued screening in 75-year-old persons after consecutive negative screenings since age 50 years will add little benefit. Individuals with continuous negative findings by

age 75 years are unlikely to have a missed adenoma at their last screening or to develop an adenoma that progresses to cancer and subsequent death from cancer after their last screening. Surveillance colonoscopies for patients with adenomas detected are continued without a stopping age. Our analysis used chronologic age rather than comorbidity-adjusted life expectancy, and the decision to stop screening in practice should consider the age and health of the patient. As a guide, life expectancy at age 75 years is 10.5 years for men and 12.5 years for women.[267]

A few findings can be explained by model differences. Both models incorporate assumptions about the adenoma-carcinoma sequence (that is, the development of colorectal cancer from adenomas), for which limited data are available to estimate the time that it takes (on average) for an adenoma to develop into preclinical cancer. For example, in the MISCAN model, the average time from adenoma development to colorectal cancer diagnosis is 10 years among individuals with diagnosed colorectal cancer (that is, dwell time), whereas in the SimCRC model, this value is about 22 years. The implications of these differences were more life-years gained with screening in general, and more favorable results for beginning screening at age 40 years, with the SimCRC model. The former implication had minimal effect on our conclusions because the relative findings were consistent across models. The latter implication resulted in eliminating the start age of 40 years from consideration. Another difference between the models is the distribution of adenomas in the colorectal tract (Table 7.1). In the MISCAN model, adenomas are assumed to have the same distribution as colorectal cancers, while the SimCRC model is calibrated to the distribution of adenomas from autopsy studies. As a result, the MISCAN model found strategies involving sigmoidoscopy to be more effective than did the SimCRC model because a larger proportion of adenomas are within the reach of the sigmoidoscope. Despite this difference, both model results found that the strategy of sigmoidoscopy every 5 years was not as effective as annual screening with a sensitive FOBT or with colonoscopy every 10 years.

There are several limitations and caveats to consider. First, we evaluated only colorectal cancer strategies requested by the USPSTF on the basis of their review of the evidence in 2002,[263] and we did not include newer screening tests, such as computed tomographic colonography or the stool DNA test.[42, 264] Second, because we were not asked to provide a cost-effectiveness analysis, we used the number of colonoscopies as a proxy for resource utilization, as well as nonfatal adverse effects from screening. However, this does not capture all resources required per scenario, although we report the numbers of non-colonoscopy tests (that is, FOBT or flexible sigmoidoscopy) required for each strategy. Third, we assumed 100% adherence with screening, follow-up (chance of undergoing diagnostic colonoscopy if a screening test result is positive), and surveillance for all scenarios to provide outcomes associated with the strategies as they were specified. In practice, adherence is much lower than 100% and varies across type of screening test. We conducted a sensitivity analysis that varied overall adherence but not differentially across strategies. We chose to evaluate strategies assuming equivalent adherence because it is uncertain whether adherence will be higher with non-invasive but more frequent testing, or invasive but less frequent testing. Because we considered 3 different adherence scenarios in Figure 7.2, readers can compare different adherence levels themselves. We emphasize that in practice adherence is critical and that ultimately the best option for a patient is the one that he or she will attend.[71, 107] In addition, issues pertaining to the implementation of a screening program, including endoscopy capacity,[165, 268, 269] professional qualification,[270, 271] insurance coverage, shared decision making, and how to increase adherence with

colorectal cancer screening,[272] are important considerations for implementing recommendations in practice.

In conclusion, our results support colorectal cancer screening with colonoscopy every 10 years, a sensitive FOBT annually, or flexible sigmoidoscopy every 5 years with a mid-interval sensitive FOBT from age 50 to 75 years. Our findings in general support the 2002 USPSTF recommendations for colorectal cancer screening, with a few exceptions. First, although there is currently no recommended stopping age for colorectal cancer screening, we found that continuing screening after age 75 in individuals who have had regular, consistently negative screenings since age 50 provides minimal benefit for the resources required. Second, we found that screening with Hemoccult II annually and flexible sigmoidoscopy alone every 5 years does not provide effectiveness similar to that of screening annually with a sensitive FOBT or every 10 years with colonoscopy. Finally, if a sensitive FOBT is used, the FOBT screening interval can be extended to 3 years when used in combination with flexible sigmoidoscopy every 5 years. These conclusions were corroborated by 2 independent microsimulation models.

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Appendix Table 1 to chapter 7: Efficient and near-efficient strategies for colonoscopy

			Outcomes per 1000 persons			
Test, Age Begin - Age Stop, Interval*	COL	Non-COL tests	LYG	ДCOL	ДLYG	ДCOL/ДLYG
MISCAN						
COL, 60-75, 20	2,175	0	156	-	-	-
COL, 50-75, 20	3,325	0	203	1,150	47	24.7
COL, 50-75, 10	**4,136**	**0**	**230**	**811**	**27**	**29.6**
COL, 50-85, 10	4,534	0	236	398	5	72.9
COL, 50-75, 5	5,895	0	254	1,362	18	74.8
COL, 50-85, 5	6,460	0	257	565	4	156.1
SimCRC						
COL, 60-75, 20	1,780	0	165	-	-	-
COL, 50-75, 20	2,885	0	246	1,106	82	13.5
COL, 50-75, 10	**3,756**	**0**	**271**	**871**	**25**	**34.7**
COL, 50-85, 10	4,114	0	273	-	-	Near-efficient[†]
COL, 50-75, 5	5,572	0	282	1,816	10	178.8
COL, 50-85, 5	6,031	0	282	459	1	975.7

COL = colonoscopy; ДCOL = incremental number of colonoscopies compared to the next-best non-dominated strategy; LYG = life-years gained compared to no screening; ДLYG = incremental number of life-years gained compared to the next-best non-dominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.

* Bold indicates recommendable strategy. Age and intervals expressed as years.

[†] Strategy yields life-years gained within 98% of the efficient frontier.

Appendix Table 2 to chapter 7: Efficient and near-efficient strategies for Hemoccult II

Test, Age Begin - Age Stop, Interval*	Outcomes per 1000 persons					
	COL	Non-COL tests	LYG	ДCOL	ДLYG	ДCOL/ДLYG
MISCAN						
Hemoccult II, 60-75, 3	681	4,434	89	-	-	-
Hemoccult II, 60-75, 2	854	5,784	105	172	16	10.6
Hemoccult II, 50-75, 3	1,033	6,941	121	-	-	Near-efficient†
Hemoccult II, 50-75, 2	1,335	9,509	149	482	44	11.0
Hemoccult II, 50-85, 2	1,513	11,162	158	-	-	Near-efficient†
Hemoccult II, 50-75, 1	**1,982**	**16,231**	**194**	**647**	**45**	**14.3**
Hemoccult II, 50-85, 1	2,186	18,409	202	203	8	25.5
SimCRC						
Hemoccult II, 60-75, 3	425	4,291	75	-	-	-
Hemoccult II, 50-75, 3	699	6,834	129	275	54	5.1
Hemoccult II, 50-75, 2	921	9,422	162	221	33	6.7
Hemoccult II, 50-75, 1	**1,456**	**16,239**	**218**	**536**	**56**	**9.6**
Hemoccult II, 50-85, 1	1,712	18,262	223	256	5	47.9

COL = colonoscopy; ДCOL = incremental number of colonoscopies compared to the next-best non-dominated strategy; LYG = life-years gained compared to no screening; ДLYG = incremental number of life-years gained compared to the next-best non-dominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.

* Bold indicates recommendable strategy. Age and intervals expressed as years.

† Strategy yields life-years gained within 98% of the efficient frontier.

Appendix Table 3 to chapter 7: Efficient and near-efficient strategies for Hemoccult SENSA

	Outcomes per 1000 persons					
Test, Age Begin - Age Stop, Interval*	COL	Non-COL tests	LYG	ДCOL	ДLYG	ДCOL/ДLYG
MISCAN						
Hemoccult SENSA, 60-75, 3	1,363	3,824	134	-	-	-
Hemoccult SENSA, 60-75, 2	1,647	4,732	149	-	-	Near-efficient†
Hemoccult SENSA, 50-75, 3	2,121	5,596	181	758	47	16.0
Hemoccult SENSA, 50-75, 2	2,584	7,014	205	463	24	19.5
Hemoccult SENSA, 50-85, 2	2,801	7,679	211	-	-	Near-efficient†
Hemoccult SENSA, 50-75, 1	**3,350**	**9,541**	**230**	**766**	**25**	**30.9**
Hemoccult SENSA, 50-85, 1	3,538	9,904	232	188	2	80.6
SimCRC						
Hemoccult SENSA, 60-75, 3	934	3,735	123	-	-	-
Hemoccult SENSA, 50-75, 3	1,587	5,554	201	653	78	8.4
Hemoccult SENSA, 50-75, 2	1,957	7,006	228	370	28	13.3
Hemoccult SENSA, 50-75, 1	**2,654**	**9,573**	**259**	**698**	**31**	**22.9**
Hemoccult SENSA, 50-85, 1	2,996	9,918	262	341	3	128.2

COL = colonoscopy; ДCOL = incremental number of colonoscopies compared to the next-best non-dominated strategy; LYG = life-years gained compared to no screening; ДLYG = incremental number of life-years gained compared to the next-best non-dominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer.

* Bold indicates recommendable strategy. Age and intervals expressed as years.

† Strategy yields life-years gained within 98% of the efficient frontier.

Appendix Table 4 to chapter 7: Efficient and near-efficient strategies for fecal immunochemical test

	Outcomes per 1000 persons					
Test, Age Begin - Age Stop, Interval*	COL	Non-COL tests	LYG	ДCOL	ДLYG	ДCOL/ДLYG
MISCAN						
FIT, 60-75, 3	1,158	4,036	129	-	-	-
FIT, 60-75, 2	1,403	5,099	144	-	-	Near-efficient†
FIT, 50-75, 3	1,769	6,090	173	611	44	14.0
FIT, 50-75, 2	2,184	7,915	198	415	25	16.5
FIT, 50-85, 2	2,396	8,896	206	-	-	Near-efficient†
FIT, 50-75, 1	**2,949**	**11,772**	**227**	**765**	**30**	**25.9**
FIT, 50-85, 1	3,155	12,582	231	206	4	49.1
SimCRC						
FIT, 60-75, 3	772	3,943	118	-	-	-
FIT, 50-75, 3	1,286	6,047	193	514	75	6.9
FIT, 50-75, 2	1,614	7,908	222	327	29	11.3
FIT, 50-75, 1	**2,295**	**11,830**	**256**	**681**	**35**	**19.7**
FIT, 50-85, 1	2,623	12,587	260	328	3	95.7

COL = colonoscopy; ДCOL = incremental number of colonoscopies compared to the next-best non-dominated strategy; LYG = life-years gained compared to no screening; ДLYG = incremental number of life-years gained compared to the next-best non-dominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer; FIT = fecal immunochemical test.

* Bold indicates recommendable strategy. Age and intervals expressed as years.

† Strategy yields life-years gained within 98% of the efficient frontier.

Appendix Table 5 to chapter 7: Efficient and near-efficient strategies for flexible sigmoidoscopy

	Outcomes per 1000 persons					
Test, Age Begin - Age Stop, Interval*	COL	Non-COL tests	LYG	ДCOL	ДLYG	ДCOL/ДLYG
MISCAN						
FSIG, 60-75, 20	1,047	917	114	-	-	-
FSIG, 60-75, 10	1,311	1,530	140	-	-	Near-efficient†
FSIG, 60-75, 5	1,491	2,617	159	-	-	Near-efficient†
FSIG, 50-75, 10	1,685	2,338	177	-	-	Near-efficient†
FSIG, 50-75, 5	**1,911**	**4,139**	**203**	**864**	**89**	**9.7**
FSIG, 50-85, 5	1,996	4,745	207	85	4	22.3
SimCRC						
FSIG, 60-75, 20	438	889	94	-	-	-
FSIG, 50-75, 20	662	1,662	147	224	53	4.2
FSIG, 50-85, 20	674	1,661	147	-	-	Near-efficient†
FSIG, 50-75, 10	808	2,455	176	146	29	5.0
FSIG, 50-75, 5	**995**	**4,483**	**199**	**187**	**22**	**8.4**
FSIG, 50-85, 5	1,064	5,088	201	68	2	38.5

COL = colonoscopy; ДCOL = incremental number of colonoscopies compared to the next-best non-dominated strategy; LYG = life-years gained compared to no screening; ДLYG = incremental number of life-years gained compared to the next-best non-dominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer; FSIG = flexible sigmoidoscopy.

* Bold indicates recommendable strategy. Age and intervals expressed as years.

† Strategy yields life-years gained within 98% of the efficient frontier.

Appendix Table 6 to chapter 7: Efficient and near-efficient strategies for flexible sigmoidoscopy plus Hemoccult SENSA

	Outcomes per 1000 persons					
Test, Age Begin - Age Stop, Interval*	COL	Non-COL tests	LYG	ДCOL	ДLYG	ДCOL/ДLYG
MISCAN						
FSIG+SENSA, 60-75, 20, 3	1,817	4,142	163	-	-	-
FSIG+SENSA, 60-75, 10, 3	1,933	4,497	171	-	-	Near-efficient†
FSIG+SENSA, 60-75, 5, 3	2,031	5,220	179	213	15	14.0
FSIG+SENSA, 50-75, 20, 3	2,658	6,192	213	-	-	Near-efficient†
FSIG+SENSA, 50-75, 10, 3	2,756	6,573	221	-	-	Near-efficient†
FSIG+SENSA, 50-75, 5, 3	**2,870**	**7,685**	**230**	**839**	**52**	**16.3**
FSIG+SENSA, 50-85, 5, 3	3,042	8,380	233	172	3	60.7
FSIG+SENSA, 50-75, 5, 2	3,142	8,588	235	100	2	62.3
FSIG+SENSA, 50-85, 10, 2	3,245	8,350	232	-	-	Near-efficient†
FSIG+SENSA, 50-85, 5, 2	3,321	9,267	237	179	2	74.3
FSIG+SENSA, 50-75, 20, 1	3,558	9,590	236	-	-	Near-efficient†
FSIG+SENSA, 50-75, 10, 1	3,591	9,738	237	-	-	Near-efficient†
FSIG+SENSA, 50-75, 5, 1	3,635	10,279	239	314	2	139.8
FSIG+SENSA, 50-85, 20, 1	3,734	9,915	238	-	-	Near-efficient†
FSIG+SENSA, 50-85, 10, 1	3,768	10,081	239	-	-	Near-efficient†
FSIG+SENSA, 50-85, 5, 1	3,808	10,611	240	172	1	154.5

Appendix table 6 to chapter 7 continued

Test, Age Begin - Age Stop, Interval*	Outcomes per 1000 persons					
	COL	Non-COL tests	LYG	ДCOL	ДLYG	ДCOL/ДLYG
SimCRC						
FSIG+SENSA, 60-75, 20, 3	956	7,763	152	-	-	-
FSIG+SENSA, 60-75, 10, 3	999	11,104	161	44	9	4.7
FSIG+SENSA, 60-75, 5, 3	1,045	10,064	169	45	8	5.5
FSIG+SENSA, 50-75, 10, 3	1,621	12,485	246	-	-	Near-efficient†
FSIG+SENSA, 50-75, 5, 3	**1,655**	11,623	**257**	**611**	**88**	**7.0**
FSIG+SENSA, 50-85, 5, 3	1,908	9,484	260	-	-	Near-efficient†
FSIG+SENSA, 50-75, 5, 2	1,994	12,265	265	338	8	41.7
FSIG+SENSA, 50-85, 5, 2	2,298	9,895	268	-	-	Near-efficient†
FSIG+SENSA, 50-75, 20, 1	2,647	10,214	270	-	-	Near-efficient†
FSIG+SENSA, 50-75, 10, 1	2,653	14,403	271	-	-	Near-efficient†
FSIG+SENSA, 50-75, 5, 1	2,666	13,593	274	673	9	75.7
FSIG+SENSA, 50-85, 20, 1	2,981	7,133	272	-	-	Near-efficient†
FSIG+SENSA, 50-85, 10, 1	2,987	5,794	274	-	-	Near-efficient†
FSIG+SENSA, 50-85, 5, 1	2,996	10,875	276	330	2	154.4

COL = colonoscopy; ДCOL = incremental number of colonoscopies compared to the next-best non-dominated strategy; LYG = life-years gained compared to no screening; ДLYG = incremental number of life-years gained compared to the next-best non-dominated strategy; MISCAN = Microsimulation Screening Analysis; SimCRC = Simulation Model of Colorectal Cancer; FSIG = flexible sigmoidoscopy; SENSA = Hemoccult SENSA.

* Bold indicates recommendable strategy. Age and intervals expressed as years.

† Strategy yields life-years gained within 98% of the efficient frontier.

Chapter 8: Discussion

In this thesis, we used microsimulation modeling to assess the effects of colorectal cancer (CRC) interventions on population health. In this chapter, we will first answer the research questions formulated in chapter 1, based on the results described in this thesis. Next, we will present the status of modeling-based decision-making in health care and identify future directions for research. This chapter ends with conclusions and recommendations.

8.1 Answers to research questions

Is there a colorectal cancer screening model that can explain the seemingly disparate results of the different screening trials?

> We were able to fit one CRC natural history model that simultaneously explains the results of the three fecal occult blood test (FOBT) trials in Minnesota, Nottingham and Funen. In this model, sensitivity of the FOBT is higher in the stage in which the cancer would have been diagnosed in the absence of screening than in earlier stages.

Microsimulation modeling is a useful tool to extrapolate the results of randomized clinical trials to other (real-world) settings. However, estimates for sensitivity and sojourn time differed widely between trials and extrapolation with the respective estimates will lead to different conclusions. We found that it is possible to explain the results of the three trials of Minnesota, Nottingham and Funen with one CRC duration and FOBT model, when correcting for differences in trial design. In this model the average duration of CRC is longer than previously estimated (6.7 years), and sensitivity of FOBT is higher (51%) in the stage of clinical diagnosis, than in earlier preclinical invasive stages (19%).

A preclinical duration of 6.7 years is longer than previous estimates of sojourn time based on these trials, and our sensitivity estimate is lower.[81, 273-275] However, we were the first to fit the stage distribution of screen-detected cases. Based on this stage comparison, we found that FOBT is mainly sensitive for cancers in the stage of clinical detection, which lasts on average 2.5 years. This latter estimate together with a sensitivity of 51% for this stage, is in line with the individual estimates by the investigators of the Nottingham and Funen trials.[80, 81] Only the sensitivity estimate from investigators of the Minnesota trial was considerably higher.[82] The weighted average of sensitivity in stage of clinical diagnosis and sensitivity in earlier stages is approximately 32%, which is in line with the sensitivity of 11-50% found in studies where FOBT accuracy is evaluated by colonoscopy as a gold standard.[36, 90-94] The approach we propose explains most of the difference between published high FOBT sensitivity estimates based on trial results versus the low estimates based on back-to-back studies with colonoscopy.

Although there is a statistical lack-of-fit to the observations (p=0.02) with this model, we would like to argue that the goodness-of-fit is satisfactory. Outliers partly explain the lack-of-fit. In the Minnesota trial, the interval cancer rate in the first year after screening is very low compared to the

rates in later years. The screen-detected CRC rate in round 3 of the Nottingham trial and rounds 2 and 7 in the Funen trial differ significantly from rates in other rounds. If these observations would have been more similar to those in adjacent rounds, the p-value would improve to a non-significant p=0.1. Furthermore, there might well be unidentified sources of heterogeneity between the trial conditions for which we did not account in the model. It is has been studied, for example, that the positivity rate of FOBT depends on season.[276]

Dividing preclinical cancers in an early phase with low FOBT sensitivity and a later phase with high FOBT sensitivity is a novel way of describing the occult blood detection process. It not only best explains observed trial outcomes but it is also biologically plausible. FOBT finds CRC because of (occult) bleeding of the tumor. Macroscopic bleeding is also important for clinical detection of CRC. About 34%-58% of CRC present with rectal bleeding.[86-89] It is very plausible that occult bleeding precedes macroscopic bleeding and thus that sensitivity of FOBT depends on time to clinical diagnosis. Interestingly the range of cancers that present with bleeding compares well with our sensitivity estimate of 51%. Despite its plausibility, this hypothesis was never tested, may be because it cannot be observed in studies (time of clinical manifestation of a disease is not known), or estimated through classical sensitivity estimation. With microsimulation, time of clinical manifestation is pseudo-observed and therefore sensitivity of the test can be varied accordingly. But also published microsimulation models have so far assumed the same sensitivity of FOBT for all preclinical CRC stages, regardless of when individual cancers become clinical.[72]

Our improved estimates can be used to better extrapolate the trial results to newer and more sensitive FOBTs, for which no randomized controlled trial results are available. Because these tests have higher sensitivity, one could argue that the screening interval could be lengthened with these tests. However, the mechanism of detection here is also aiming at occult blood, so it is likely that these more sensitive tests are also mainly sensitive for lesions shortly before clinical diagnosis. Therefore also with a higher sensitivity, it will remain important to screen with FOBT frequently. Our results also have implications for endoscopy screening. Although the attention of endoscopy is often on detection and treatment of pre-cancerous adenomas, the added effectiveness due to detection of cancers in a (very) early stage is stressed by this analysis.

How much can current preventive and curative interventions reduce colorectal cancer mortality?

Currently available interventions for risk factor modification, screening, and treatment have the potential to further reduce CRC mortality by almost 50% in 20 years. However, without action to increase the uptake of current effective interventions, the reduction in CRC mortality may be only 17%.

Randomized controlled trials have shown that adjuvant chemotherapy and FOBT screening reduce CRC mortality. Furthermore, observational studies suggest that endoscopic screening and healthy lifestyle also have a reducing effect on CRC mortality. We have estimated that with these currently available interventions CRC could be reduced in the U.S. by almost 50% in the coming 20 years. In the short-term, increasing use of chemotherapy has the biggest impact on CRC mortality. In the longer-term, further dissemination of screening contributes most, followed by changing life-style.

These are positive results, not only for the U.S., but also for the Netherlands. In the U.S. currently almost 50% of the population are already being screened.[108] In the Netherlands no screening for CRC has been introduced so far. This means that the potential impact of introducing screening and reaching a high uptake is even bigger than in the U.S..

However, the reduction in CRC mortality in both the U.S. and the Netherlands could also be substantially less (estimated at 17%), if we are not able to further increase healthy behavior, participation in screening and use of new chemotherapies. Even increasing screening participation may turn out to be difficult to accomplish. Each of the established screen tests has its drawbacks besides its advantages. FOBT screening is simple and non-invasive but also not very sensitive.[28, 81, 82, 157] Sigmoidoscopy screening only visualizes half of the colorectum and colonoscopy screening is highly invasive and not without risk. Also, colonoscopy requires burdensome preparation. Currently, almost 50% of the U.S. population does not participate in CRC screening, for a large part because of these barriers.[108] Therefore new tests are being developed attempting to take away these barriers, such as stool DNA testing and CT Colonography (CTC).

What is the cost-effectiveness of new colorectal cancer screen tests, such as CT colonography?

CTC can be a cost-effective alternative method of colorectal cancer screening in the general population, if follow-up with optical colonoscopy is restricted to those with polyps of 6 mm and larger and if CTC costs less than 43% of colonoscopy costs.

CTC is a promising developing technique for CRC screening, combining high sensitivity for larger polyps and cancer with a non-invasive procedure. However, for a test to be implemented for mass screening, it need not only be effective but also cost-effective. We found that at costs equal to colonoscopy screening, CTC currently is not a cost-effective test for CRC screening. However, if CTC costs could be reduced to less than half of colonoscopy costs, CTC would become a cost-effective alternative to colonoscopy screening, when it would be offered every 5 years and follow-up would be restricted to lesions of 6 mm and larger.

Several other studies have been published on the cost-effectiveness of CTC screening in the general population.[170-172, 202] In all these studies, the threshold costs for CTC screening were higher than in our study. An important reason for this is that where the other studies compared CTC only to 10-yearly colonoscopy, we allowed different colonoscopy intervals. Comparison with other colonoscopy intervals is needed to ascertain that CTC screening is not dominated by colonoscopy screening.

Because the Centers for Medicare and Medicaid Services (CMS) do not yet reimburse CTC screening, there currently is no reimbursement rate for CTC screening. However, diagnostic CT scans of the abdomen and pelvis are being reimbursed. For our cost-effectiveness analysis on CTC screening for CMS,[277] we used the sum of the rates for these two procedures together with the rate of postprocessing of the images as a proxy for the costs of a screening CTC. This yielded costs for CTC of $610, which are considerably higher than the required 43% of colonoscopy costs estimated in this study. However, because CTC is a one-step procedure, whereas a CT scan of the abdomen and pelvis are two independent procedures, economies of scale will apply, up to a 50% reduction in the costs of the second procedure (Joel Brill, M.D. Predictive Health of Phoenix, AZ, personal communication).

This would reduce CTC costs to $492. The development of computer-assisted reading of the images and detection of lesions has potential for decreasing radiologists reading time and therewith reducing costs.[203] If this development would be able to decrease the costs of postprocessing by 50%, CTC costs would reduce to $425. At 64% of colonoscopy costs, this would still be higher than the 43% estimated here. However, our current estimate for colonoscopy costs does not include anesthesia costs, whereas there is evidence that in 29% of colonoscopies anesthesia is being reimbursed and this level Is increasing.[277] A CTC cost level of $425 is approximately 56% of colonoscopy costs with anesthesia costs included. The potential introduction of CTC without cathartic preparation is expected to further reduce costs.[204, 205] All together, a costs level of 43% of colonoscopy costs may become feasible.

CTC screening is a non-invasive alternative to colonoscopy screening, and is not associated with the major complications of colonoscopy such as perforations, serosal burns, and bleeds.[58, 187-190] A recent study comparing CTC and colonoscopy for CRC screening,[200] reported seven serious adverse events in 3,163 people undergoing colonoscopy, and no complications in 3,120 people undergoing CTC. On the other hand, CTC is associated with exposure to radiation, which we did not consider in the current analysis. The excess cancer risk from 5-yearly CTC screening from age 50 to age 80 using typical current scanner techniques is about 0.47%.[201] This estimate is controversial, because it was based on simulation calibrated to atomic bomb survivors. However if true, this estimate will lead to life-years lost due to CTC which are not negligible compared to the life-years gained. We did not take these excess cancer cases into account, because there is good evidence that radiation dose with CTC can be reduced by at least a factor of 5 (and perhaps as much as 10), while still maintaining sensitivity and specificity for polyps larger than approximately 5 mm.[201] With such a dose reduction, excess risk of cancer from CTC becomes very small.

In a study for the Agency of Health Research and Quality (AHRQ), we evaluated the cost-effectiveness of stool DNA testing.[42] The stool DNA test strategies considered were all more costly and less effective than an alternative strategy or a combination of other strategies. The fact that stool DNA testing, based on evidence available to date, was not cost-effective when compared to the other CRC screening tests had been anticipated, given that the stool DNA test was not more sensitive or specific than Hemoccult SENSA and yet almost 80 times as expensive. Although CTC and stool DNA testing were not cost-effective compared to other screening tests, the costs per life-year gained compared to no screening were well below $50,000. Studies have shown that currently all available CRC screening tests are cost-effective compared to no screening.

Will colorectal cancer screening become cost-saving with the rapidly increasing treatment costs of colorectal cancer?

With the rapidly increasing treatment costs, the potential treatment savings from screening increase substantially and become larger than the screening costs.

Our calculations support the hypothesis that FOBT and sigmoidoscopy screening will become cost-saving in the near-future if treatment costs increase rapidly and screening costs remain stable. Observations in the recent past confirm this trend. From 1990-1994 to 1998-2003, treatment costs

per case have increased by up to 200% depending on the stage of disease,[191, 212] while unit screening costs have not increased.[42, 209] The assumed increase in treatment costs from the "Present" to the Near-future scenario" used for our model is uncertain. We assumed a lower increase than the observed increase from the "Past" to the "Present scenario". For the "Near-future" scenario, we have accounted for differences in price between the current chemotherapies (5-FU and FOLFIRI) and newly available chemotherapies (FOLFOX and bevacizumab).

Of course the new chemotherapies not only increase costs but also decrease CRC mortality, by postponing or sometimes even preventing CRC death. Because of this better survival, fewer people die of CRC and less life-years are to be gained by screening. Improved survival was incorporated in our analysis, but its effect on life-years gained by screening turned out to be minimal. The shifting balance between screening costs and treatment savings of CRC screening with the introduction of new chemotherapies reflects the higher costs per life-year saved of these new treatments. Generally, cost-effectiveness thresholds for treatments are much higher than for secondary prevention. It is therefore good to realize that with the introduction of expensive chemotherapies with high costs per life-year gained, secondary prevention becomes more and more cost-effective and may be even essential to keep health care budgets manageable.

Can individualization of screening guidelines by gender and race make colorectal cancer screening more efficient?

Only marginally. Uniform and individualized screening are comparable in costs and effects in the total population, with individualized guidelines being slightly more effective and slightly less costly than uniform guidelines. However, individualized guidelines can decrease health disparities between blacks and whites.

In the U.S., blacks have higher CRC mortality than whites and men have higher mortality than women. Debate has arisen whether screening recommendations for these groups should therefore not be individualized.[223] We have contributed to this discussion with a formal decision analysis comparing individualized guidelines with uniform guidelines. We found that with individualized guidelines blacks should be offered more intensive screening than whites. Individualization will contribute to reducing health disparities between blacks and whites. Although the costs and life-years gained in the total population were only marginally better than with uniform guidelines, the feasibility and acceptability of individualized guidelines should be explored.

Age-specific CRC incidence and mortality in men reaches levels of risk comparable to women four to eight years later in life.[256] Also, more women than men need to be screened for the detection of one advanced neoplasia.[189, 253, 257] Therefore, one would expect that men need earlier and more intensive screening than women. However, our results show that the cost-effective individualized policies for men and women are comparable. This is due to longer life-expectancy of women. Although women have fewer advanced adenomas than men, more of those adenomas can evolve into CRC during the longer lifetime. This makes the number of cancers that can be prevented by screening similar for men and women. Our finding of similar screening strategies is supported by the fact that the absolute number of CRC cases in men and women is comparable.[258]

For Europe, our findings suggest that CRC screening programs probably do not need to be individualized. There is no large black minority population like in the U.S. and data on other minorities in the U.S. suggest that other ethnic groups mainly have lower CRC risk than the white population.[260] The data on these groups are too sparse to do an actual decision analysis, but they do suggest that offering minorities in Europe the same CRC screening recommendation as the majority population is, if anything, on the safe side.

What are appropriate ages and intervals for colorectal cancer screening?

Our results support the currently recommended screening strategies of 10-yearly colonoscopy, and annual screening with a sensitive FOBT, both starting at age 50. If FOBT is done in combination with sigmoidoscopy, sigmoidoscopy can best be performed every 5 years and FOBT every 2-3 years. Our results further support stopping screening after age 75 in individuals without adenomas detected.

The United States Preventive Services Taskforce (USPSTF) requested a decision analysis of age to begin, age to stop, and intervals of screening to address appropriate timing of CRC screening in their recommendations. We used two independently developed models to address this question. Both models agreed that the life-years gained from screening after age 75 were not in balance with the incremental colonoscopies required. The models also agreed that the currently recommended intervals for colonoscopy and FOBT screening were appropriate and that the interval for FOBT screening in combination with sigmoidoscopy could be extended to 3 years. However, the models disagreed on the benefit of starting screening at age 40. The evidence on the determinant of start age 40, the duration of the adenoma-carcinoma, is weak. Therefore, we decided to focus on start ages 50 and 60. In that case both models agreed that starting at age 50 was preferred over starting at age 60.

The recommendation to stop CRC screening after the age of 75 is different from the prior recommendations in the U.S., which had no stop age.[71, 107] The two models consistently found that continued screening in those who have had no adenomas or CRC detected by age 75 after consecutive consistent negative screenings since age 50 will add little benefit but could confer risk of colonoscopic complications. Surveillance colonoscopies for those with adenomas or CRC detected are continued without a stopping age. The explanation for this finding is that individuals with consistent negative findings by age 75 are unlikely to either develop adenomas or to have a newly developed adenoma, post age 75, transform into a CRC causing early death during the remaining lifetime. It has to be noted that our analyses used chronological age rather than comorbidity-adjusted life expectancy. The actual stopping rule should consider the comorbidities of the individual and the individual's anticipated life expectancy. As a guide, life expectancy at age 75 is 10.5 years for men and 12.5 years for women and at age 85 its 5.9 years and 7.0 years for men and women, respectively.[267]

An interesting finding of this study is that annual screening with sensitive FOBT was equally effective as 10-yearly colonoscopy screening, provided equally high adherence. However, we would not recommend one test over the other test based on these modeling results. Because no results from

randomized controlled trials on the efficacy of endoscopy screening are available yet, it may turn out that we have underestimated the potential of endoscopy to prevent CRC. On the other hand, it is certainly not unrealistic for annual screening with a sensitive FOBT to be (almost) as effective as 10-yearly colonoscopy screening. Test sensitivity of these tests for cancer and large adenomas is considerably higher than of Hemoccult II,[42] and because the test is repeated every year the program sensitivity for cancer and large adenomas may well reach levels equal to colonoscopy screening. However, if sensitive FOBTs systematically miss certain lesions, effectiveness will not be comparable to colonoscopy screening. Detection rates in repeat screening rounds are required to determine if this is the case.

8.2 Modeling-based decision making in health care

The chapters in this thesis again show how microsimulation modeling can be used to answer a variety of research questions on the natural history of disease, population trends and cost-effectiveness of interventions. It is important to realize that models are only as good as the assumptions that go in. Although CRC has been studied extensively, many parameters are still uncertain. An important parameter for the effectiveness of screening is the sojourn time of preclinical (i.e. undiagnosed) screendetectable disease (i.e. the duration of the adenoma-carcinoma sequence). Based on the difference in age of onset of adenomas and age of onset of cancers in FAP-patients, the duration of the adenoma-carcinoma sequence was estimated to be 10 years.[278] It is unknown if this estimate is valid for average-risk patients and what the variation is around this duration. Randomized controlled trials on endoscopy screening are underway and will provide important information on these parameters.[55-57] Until these results become available, thorough sensitivity analyses are required to assess the sensitivity of model predictions to its assumptions.

Model structure is also an important determinant of model predictions, but it is generally hard to assess its effect with one particular model. Therefore the Cancer Intervention and Surveillance Modeling Network (CISNET) was established to facilitate comparative analyses of the same research questions by independently developed models. CISNET has given a big impulse to collaborations between scientific modelers and has greatly strengthened modeling expertise in this way. As such, the CISNET program has been applauded for its role in collaborative modeling by leading decision analysts.[279]

Chapter 7 is an example of such a comparative modeling analysis. Comparable results from different models strengthen modeling conclusions. But differences in results are also valuable. They show where data is lacking to inform the models and what the plausible range of outcomes is given this data uncertainty. From the CISNET analyses, the modelers have learnt that their models differ substantially in the average dwelling time that an adenoma has been present before it actually is diagnosed as clinical cancer. The reason for this is that good data are lacking to inform what the true dwelling time is. Despite this substantial difference in dwelling time assumptions, the SimCRC (University of Minnesota) and MISCAN models agreed on the optimal stopping age, interval and set of tests to be recommended. The models only differed with respect to the optimal age to begin screening (chapter 7). So even though the results from two models were somewhat different, still useful recommendations could be based on the results.

Despite their usefulness, models and their outcomes are still distrusted. Microsimulation models are complex. This makes it hard for non-modelers to understand them and even modelers have to work hard to understand each other's models. To many clinicians and policy makers, models are black boxes. They agree that the answers that come from models can be useful, but they have no way of validating to what extent these answers can actually be trusted. The discrepancy between results from different modeling research groups in literature has also contributed to the distrust.[72] Clinicians and policy makers prefer statistics on actual data to extrapolation of data with models. These statistics keep their value, but given the limited amount of time and resources available in order to empirically investigate every possible screening option, extrapolation of trial results with models seems unpreventable and desirable. Therefore, there lies an important task for modelers to try and make their models more open and understandable for the other scientific researchers, clinicians and decision makers. In the CISNET group, we have made a first effort at this by documenting our models extensively in a standardized model profile.[280]

Recently, there has been a tendency towards using models in health care decision making, especially concerning screening. Amongst others based on MISCAN results, CMS have determined that immunochemical FOBT would be reimbursed as a screening test at costs of $22.22.[281] The SimCRC and MISCAN models were also used to inform CMS on the cost-effectiveness of stool DNA screening[42] and CTC screening.[277] Finally, the joint analysis of the MISCAN and SimCRC microsimulation models in chapter 7 was used to inform new colorectal screening guidelines of the USPSTF.[210] In the fields of breast cancer and cervical cancer screening, different models are now also being used to inform the USPSTF guidelines. We are in favor of this development, because despite the uncertainties around model assumptions and parameters, using model outcomes for these decisions is better than using expert opinion only.

8.3 Future directions

The fields of CRC screening and care are rapidly developing. Many countries are in the process of implementing CRC screening programs, new screening tests are being developed and evaluated, and new chemotherapies become available. With all these developments it is important to conduct evidence-based medicine. Models will remain important for extrapolating the evidence beyond trial results.

There are several important issues that need to be resolved in the coming years:

1. *Determining efficient guidelines for surveillance after polypectomy*
   The Dutch guidelines for surveillance after polypectomy are only based on the number of adenomas detected at the last colonoscopy. Data for more specific risk predictors were not available at the moment the guidelines were specified. With the probable introduction of a national CRC screening program in the Netherlands, the number of patients with polypectomy will significantly increase. It is therefore very important to have an efficient guideline. Meanwhile, Dutch gastroenterologists are unsatisfied with the guidelines.[282] Consequently, we are collecting retrospective data on patient and adenoma characteristics at baseline colonoscopy. We will use the MISCAN-Colon model to analyze these data and determine optimal guidelines for surveillance after polypectomy based on these characteristics.

2. *Estimating potential for reducing health disparities*
   Health disparities are an important issue, not only in the United States but in many countries in Europe as well. For the U.S., we have shown that according to individualized guidelines blacks should be screened earlier and with higher frequency than whites. Disparities exist between blacks and whites in risk factors, screening uptake and chemotherapy use.[108, 134, 283] Taking away these disparities together with individualized guidelines, could reduce the disparity in CRC mortality substantially. With the MISCAN-Colon model, we want to evaluate how much difference this would make, as input for further decision making.

3. *Determining when to stop screening*
   In chapter 7 we showed that continuing CRC screening after age 75 does not provide many additional life-years gained for the resources required. However, not every 75-year old has the same life-expectancy. The stop age of screening should not be so much based on chronological age, but on an individual's remaining life-expectancy. The U.S. National Cancer Institute has developed life tables based on co-morbidity status. With these life tables, we can use the MISCAN-Colon model to determine the optimal age to stop screening based on co-morbidity status of the patient.

4. *Effect of further individualization on cost-effectiveness of screening*
   In chapter 6, we found that individualization of guidelines by gender and race did not improve the cost-effectiveness of CRC screening substantially. However, many more risk and protective factors exist for CRC, diversifying the CRC risk of individuals. In the current development towards personalized medicine, an individualized screening recommendation is becoming more feasible and desirable. We can use the MISCAN-Colon model to determine how further individualization of CRC screening will affect its effectiveness and cost-effectiveness.

5. *Comparing cost-effectiveness of available screen modalities*
   In chapters 5 and 7, we have already considered costs and effects of different CRC screening tests. However, the main focus of these papers was not to compare the cost-effectiveness of the established screen tests. We deliberately have not addressed this question yet for two reasons. First, the effectiveness of endoscopy screening has not been established yet, so it is uncertain whether the estimated mortality reduction from the model is realistic. Second, the relative cost-effectiveness of different CRC screening tests will be highly dependent on the average dwelling time from adenoma to carcinoma. In the coming years, results from three randomized sigmoidoscopy trials are expected. These trials will not only provide estimates of the mortality reduction from sigmoidoscopy screening, but also the rate of interval cancers after a negative and positive sigmoidoscopy. These data will provide the model with estimates of the average dwelling time between the development of an adenoma and the diagnosis of a carcinoma. Once the model has been validated against these data, the model is better suited for a comparative cost-effectiveness analysis of CRC screening tests.

8.4 Conclusions and recommendations

In this thesis we have used the MISCAN-Colon microsimulation model to answer a number of research questions. Based on the results, we conclude that:

- The duration of preclinical CRC is longer than previously estimated (nearly 7 years).
- Sensitivity of FOBT is higher in the stage in which the cancer would have been diagnosed in the absence of screening than in earlier stages.
- Current interventions have the potential to reduce CRC mortality by 50% in the next 20 years.
- CRC screening is highly cost-effective compared to no screening. In the near-future it can become cost-saving.

Our results also support the following recommendations:

- CTC screening should not be recommended for screening the average-risk population for CRC, unless unit costs are substantially lower than for colonoscopy.
- Individualized guidelines could decrease health disparities between blacks and whites. The acceptability and feasibility of individualized guidelines should be explored.
- Good options for CRC screening are screening from age 50 to age 75 with either a sensitive FOBT annually, 10-yearly colonoscopy or 5-yearly sigmoidoscopy in combination with FOBT every 2-3 years.

Summary

Colorectal cancer (CRC) is the second leading cause of cancer death in the Netherlands and other developed countries. Each year, almost 10,000 cases are newly diagnosed in the Netherlands and over 1 million worldwide. About half of the patients die of the disease. CRC deaths can be prevented. Seventy percent of colon cancers in a cohort of middle-aged men in the U.S. potentially would be preventable by modifying risk factor behavior, such as smoking and lack of physical activity. Randomized controlled studies have shown that fecal occult blood testing (FOBT) decreases CRC mortality by 11% to 33%, while case-control studies suggest a larger reduction from endoscopy screening. Recent breakthroughs in treatment have lengthened the median survival of patients diagnosed with metastatic CRC from 6 months (without any chemotherapy) to 20 months (with cytotoxic and targeted chemotherapy). Similar improvements have been reported for patients with earlier disease stages.

Despite the proven mortality reduction since 1996, CRC screening with FOBT has not been adopted in the Netherlands yet. Most other European countries have also not implemented a national screening program for CRC until recently. The screening strategy implemented differs between countries, reflecting uncertainty about the optimal screening program.

Once randomized controlled trials have determined the efficacy of a type of screening test, microsimulation models can extrapolate the trial results to different screening ages and intervals. Moreover, models can be used to determine comparative (cost-) effectiveness of different tests and estimate the burden of a CRC screening program on available capacity and resources. In this thesis, we have used the MISCAN-Colon microsimulation model to inform policy makers on which test strategies to conduct by assessing the effect of CRC screening on population health. The work in this thesis was conducted as part of the Cancer Intervention and Surveillance Modeling Network (CISNET).

Synthesis of FOBT trial results

Sensitivity of guaiac FOBT screening has been estimated individually for each screening trial, but these estimates differ from 54-59% for the Nottingham trial, 62% for the Funen trial, to 94-96% for the Minnesota trial, all addressing the same test (Hemoccult II). Consequently, using these estimates to make predictions for the effects of FOBT screening beyond a trial setting, will lead to diverging conclusions concerning the (cost-) effectiveness of FOBT screening and the optimal interval and age range for screening. In chapter 2, we therefore used the MISCAN-Colon model to estimate the preclinical CRC duration and sensitivity for unrehydrated FOBT simultaneously from the data of these three trials. In addition to two usual hypotheses on the sensitivity of FOBT, we tested a novel hypothesis where sensitivity is linked to the stage of clinical diagnosis in the situation without screening. This novel hypothesis gave the best fit between expected and observed outcomes. Sensitivity of FOBT was 51% in the stage of clinical diagnosis but only 19% in earlier stages. The

average duration of preclinical CRC, including the early stages with low sensitivity, was estimated at 6.7 years under this hypothesis.

Current interventions for CRC mortality

Although CRC is the second leading cause of cancer death in the U.S., available interventions to reduce CRC mortality are disseminated only partially throughout the population. Chapter 3 assessed the potential reduction in CRC mortality that may be achieved through further dissemination of current interventions for risk factor modification, screening, and treatment. Without changes in risk behavior, screening use, and availability of treatment after 2000, the age-adjusted CRC mortality rate would decrease by 17% by the Year 2020. If the 1995 to 2000 trends continue, then the projected reduction in mortality would be 36%. However, if overall favorable trends in the prevalence of risk factors could be improved above continued trends, if screening use increased to 70% of the target population, and if the use of chemotherapy increased among all age groups, then a 49% reduction would be possible. Screening drove most (23%) of the projected mortality reduction with these optimistic trends; however, decreasing risk factors (16%) and increasing use of chemotherapy (10%) also contributed substantially.

Cost-effectiveness of developing screen tests

FOBT is a cheap and non-invasive test, but it leaves many cancers undetected. Endoscopy is highly sensitive for CRC and adenomas, but costly, not without risk of complications, and people are hesitant to undergo these invasive and burdensome tests. Therefore new tests are being developed aiming at increasing sensitivity for adenomas and cancers, without losing on patient acceptance. CT colonography (CTC) and stool DNA are two examples of such tests. In Chapter 4, we have evaluated the cost-effectiveness of CTC screening and estimated the threshold costs for which the test would be cost-effective compared to colonoscopy screening. We found that CTC can be a cost-effective alternative for CRC screening in the general population if offered every 5 years, with diagnostic follow-up restricted to those with polyps of 6 mm and larger and CTC costs less than 43% of colonoscopy costs. In an analysis for the Centers for Medicare and Medicaid Services (CMS), we evaluated the cost-effectiveness of stool DNA testing. All stool DNA test strategies considered were dominated by other recommended CRC screening tests.

Developments in the cost-effectiveness of CRC screening

Treatment costs for CRC, especially in advanced stages, have recently increased rapidly because of the introduction of new chemotherapy regimens and the wider application of surgery for metastases. Screening costs on the other hand have remained stable. In chapter 5, we have estimated the effect of the introduction of the new drug treatments on the costs and savings of CRC screening. The widespread use of new chemotherapies approximately doubled the treatment savings from prevented CRC and CRC deaths by screening. As a consequence, the savings with Hemoccult II ($1,387 per individual in the population), immunochemical FOBT ($1744), sigmoidoscopy ($1,695) and the combination of sigmoidoscopy with FOBT ($1,919) became larger than the screening costs ($859, $1,565, $1,691 and $1,882 per individual respectively). Colonoscopy did not become cost-saving, but the total net costs of this strategy decreased substantially from $1,422 to $413 per individual in the population.

Individualization of CRC screening

Given the differences in CRC mortality by gender and race, debate has arisen whether screening guidelines should be individualized accordingly. However, there was no formal decision analysis concerning how guidelines should be individualized and whether this would be beneficial. In chapter 6, we have provided inputs to this debate by determining what individualized colonoscopy screening guidelines by gender and race should be for the average-risk population and compare their effectiveness and cost-effectiveness to uniform guidelines for all. With individualized guidelines, blacks began screening 6 years earlier with a 1 year shorter interval compared to whites. The individualized policies were essentially the same for men and women, because the higher CRC risk in men is offset by their shorter life-expectancy. The costs and effects of individualized screening were marginally better than of uniform screening in the total population. However, with individualized screening more life-years were saved in the black population, contributing to a decrease in health disparities between blacks and whites.

Informing USPSTF recommendations

In July 2002, the U.S. Preventive Services Task Force (USPSTF) concluded that there was sufficient evidence to recommend strongly that all average-risk adults 50 years of age and older should be offered CRC screening. However, the logistics of screening, such as the type of screening test, screening interval, and age at which to stop screening, were not evaluated in terms of the balance of benefits and potential harms. The USPSTF has again addressed recommendations for CRC screening with a systematic review of the evidence on screening tests. The USPSTF also requested a decision analysis to project and compare expected outcomes of various strategies for CRC screening. In chapter 7, we used the MISCAN-Colon and SimCRC models in a comparative modeling approach to compare life-years gained relative to the use of tests, as a proxy for resource use of different strategies for CRC screening. Beginning screening at age 50 years was better than at age 60. Decreasing the stop age from 85 to 75 years decreased life-years gained by 1% to 4%, whereas colonoscopy use decreased by 4% to 15%. Assuming equally high adherence, 4 strategies provided

similar life-years gained: colonoscopy every 10 years, annual testing with a sensitive FOBT (Hemoccult SENSA or fecal immunochemical test), and sigmoidoscopy every 5 years with mid-interval sensitive FOBT. Hemoccult II and flexible sigmoidoscopy every 5 years on their own were less effective.

Conclusions and recommendations

- The duration of preclinical CRC is longer than previously estimated (nearly 7 years).
- Sensitivity of FOBT is higher in the stage in which the cancer would have been diagnosed in the absence of screening than in earlier stages.
- Current interventions have the potential to reduce CRC mortality by 50% in the next 20 years.
- CRC screening is highly cost-effective compared to no screening. In the near-future it can become cost-saving.
- CTC screening should not be recommended for screening the average-risk population for CRC, unless unit costs are substantially lower than for colonoscopy.
- Individualized guidelines could decrease health disparities between blacks and whites. The acceptability and feasibility of individualized guidelines should therefore be explored.
- Good options for CRC screening are screening from age 50 to age 75 with either a sensitive FOBT annually, 10-yearly colonoscopy or 5-yearly sigmoidoscopy in combination with FOBT every 2-3 years.

Samenvatting

Dikkedarmkanker (DDK) is de tweede doodsoorzaak aan kanker in Nederland en andere Westerse landen. Elk jaar worden bijna 10,000 mensen in Nederland gediagnosticeerd met DDK en wereldwijd zijn dat meer dan 1 miljoen mensen. Ongeveer de helft van deze mensen overlijdt aan de ziekte. DDK sterfte kan worden voorkomen. Zeventig procent van DDK in mannen van middelbare leeftijd in de Verenigde Staten kan voorkomen worden door het veranderen van risicogedrag, zoals roken en gebrek aan lichaamsbeweging. Gerandomiseerde studies hebben aangetoond dat fecaal testen op occult bloed (FOBT) DDK sterfte met 11% tot 33% kan terugdringen, terwijl case-control studies zelfs een groter effect van endoscopie screening laten zien. Recente doorbraken in behandeling hebben de gemiddelde overleving van patiënten met metastases verlengd van 6 maanden (zonder chemotherapie) tot 20 maanden (met cytotoxische en gerichte chemotherapie). Soortgelijke verbeteringen zijn gerapporteerd voor mensen met vroegere DDK stadia.

Ondanks de bewezen sterftereductie sinds 1996, is DDK screening met FOBT nog niet ingevoerd in Nederland. De meeste andere Europese landen hebben ook pas sinds kort een nationaal screening programma voor DDK geïmplementeerd. De gekozen screenstrategie verschilt tussen landen, omdat er onzekerheid bestaat over het optimale screenprogramma.

Wanneer gerandomiseerde studies de effectiviteit van een type screentest hebben vastgesteld, kunnen microsimulatiemodellen de bevindingen uit de studies extrapoleren naar andere leeftijdsgrenzen en screenintervallen. Bovendien kunnen modellen gebruikt worden om de kosteneffectiviteit van een test ten opzichte van andere tests te berekenen en in te schatten welke impact een screenprogramma heeft op beschikbare capaciteit en middelen. In dit proefschrift hebben we het MISCAN-Colon microsimulatie model gebruikt om beleidsmakers te informeren welke screenstrategieën in te voeren door het effect van DDK screening op de volksgezondheid te bepalen. De analyses in dit proefschrift zijn tot stand gekomen als onderdeel van het Cancer Intervention and Surveillance Modeling Network (CISNET).

Synthese van resultaten FOBT studies

De sensitiviteit van guaiac FOBT screening is individueel geschat voor elk van de uitgevoerde screenstudies, maar deze schattingen verschillen van 54-59% voor de Nottingham studie, 62% voor de Funen studie, tot 94-96% voor de Minnesota studie, terwijl alle schattingen over dezelfde test gaan (Hemoccult II). Gebruik van deze schattingen om voorspellingen te doen voor de effectiviteit van FOBT screening buiten de studie situatie, leidt tot verschillende conclusies over de (kosten-) effectiviteit van DDK screening en het optimale screeninterval en -leeftijden. In hoofdstuk 2, hebben we daarom het MISCAN-Colon model gebruikt om de preklinische DDK duur en de sensitiviteit van ongerehydrateerde FOBT te schatten op basis van de resultaten van de drie trials tegelijkertijd. Naast twee gebruikelijke hypotheses voor de sensitiviteit van FOBT, hebben we ook een nieuwe hypothese getest waar de sensitiviteit afhangt van het stadium van klinische diagnose in de situatie zonder screening. Deze nieuwe hypothese gaf de beste fit tussen gemodelleerde en geobserveerde uitkomsten. De sensitiviteit van FOBT was 51% in het stadium van klinische diagnose maar slechts

19% in eerdere stadia. De gemiddelde duur van preklinische DDK, inclusief de vroegere stadia met lage sensitiviteit, is geschat op 6.7 jaar bij deze hypothese.

Beschikbare interventies voor DDK sterfte

Hoewel DDK de tweede doodsoorzaak aan kanker is in de Verenigde Staten, worden de beschikbare interventies om DDK sterfte te voorkomen slechts gedeeltelijk benut. In hoofdstuk 3 hebben we onderzocht wat de mogelijke reductie in DDK sterfte zou zijn, wanneer beschikbare interventies op het gebied van aanpassen van risicogedrag, screening en behandeling op grotere schaal in de bevolking toegepast zouden worden. Zonder veranderingen in risicogedrag, screening opkomst of gebruik van behandeling na 2000, zou de gestandaardiseerde DDK sterfte met 17% afnemen tot en met het jaar 2020. Als de trends tussen 1995 en 2000 doorzetten, bedraagt de verwachte sterftereductie 36%. Echter, wanneer de gunstige trends in de prevalentie van risicofactoren verder zouden verbeteren, screening opkomst zou toenemen tot 70% van de doelgroep en het gebruik van chemotherapie toe zou nemen onder alle leeftijdsgroepen, is een sterftereductie van 49% mogelijk. Screening leverde de belangrijkste bijdrage (23%) aan de voorspelde sterftereductie met deze optimistische trends; echter, ook de bijdragen van verminderd risicogedrag (16%) en toegenomen gebruik van chemotherapie (10%) waren substantieel.

Kosteneffectiviteit van screentests in ontwikkeling

FOBT is een goedkope en niet-invasieve test, maar FOBT mist ook veel kankers. Endoscopie is zeer gevoelig voor DDK en adenomen, maar ook kostbaar, en niet zonder risico op complicaties. Veel mensen zijn dan ook huiverig om deze invasieve en belastende test te ondergaan. Daarom worden nieuwe DDK screentests ontwikkeld die beogen de sensitiviteit voor adenomen kankers te vergroten, zonder bereidheid van mensen te verliezen om de tests te ondergaan. CT Colonographie (CTC) en stool DNA zijn twee voorbeelden van zulke tests. In hoofdstuk 4 hebben we de kosteneffectiviteit van CTC screening geëvalueerd en de drempelkosten geschat waarvoor de test kosteneffectief zou zijn in vergelijking tot colonoscopie screening. We hebben aangetoond dat CTC een kosteneffectief alternatief kan zijn voor DDK screening in de algemene bevolking wanneer de test iedere vijf jaar wordt aangeboden, diagnostische follow-up beperkt wordt tot mensen met poliepen 6 mm of groter en CTC minder dan 43% van colonoscopie kosten kost. In een analyse voor de Centers for Medicare & Medicaid Services, hebben we de kosteneffectiviteit van stool DNA testen geëvalueerd. Alle onderzochte stool DNA test strategieën werden gedomineerd door andere aanbevolen DDK screentests.

Ontwikkelingen in de kosteneffectiviteit van DDK screening

Behandelkosten voor DDK, vooral in vergevorderde stadia van de ziekte, zijn de afgelopen tijd snel toegenomen met de introductie van nieuwe chemoterapieën en het vaker toepassen van chirurgie voor metastasen. De screenkosten zijn echter stabiel gebleven. In hoofdstuk 5 hebben we het effect geschat van de introductie van de nieuwe chemotherapieën op de kosten en besparingen van DDK screening. Uitgebreid gebruik van nieuwe chemotherapieën verdubbelde de besparingen in behandelkosten door voorkomen DDK en DDK sterfte door screening. Daardoor werden de besparingen met Hemoccult II ($1,387 per individu), immunochemische FOBT ($1744), sigmoidoscopie ($1,695) en de combinatie van sigmoidoscopie en FOBT ($1,919) groter dan de screenkosten (respectievelijk $859, $1,565, $1,691 and $1,882 per individu). Colonoscopie werd niet kostenbesparend, maar de totale netto kosten van deze strategie namen substantieel af van $1,422 tot $413 per individu.

Individualisatie van DDK screening

Vanwege de verschillen in DDK sterfte tussen mannen en vrouwen en blanken en zwarten, is discussie ontstaan of screenaanbevelingen niet geïndividualiseerd zouden moeten worden naar geslacht en ras. Er is echter geen formele analyse geweest om inzicht te verkrijgen hoe de aanbevelingen geïndividualiseerd zouden moeten worden en of dit überhaupt iets op zou leveren. In hoofdstuk 6, hebben we input aan deze discussie gegeven door te bepalen wat geïndividualiseerde aanbevelingen naar geslacht en ras zouden moeten zijn en de (kosten-)effectiviteit van geïndividualiseerde aanbevelingen te vergelijken met die van uniforme aanbevelingen voor iedereen. Met geïndividualiseerde aanbevelingen begonnen zwarten 6 jaar eerder met screenen met een 1-jaar korter interval vergeleken met blanken. De geïndividualiseerde aanbevelingen waren vergelijkbaar voor mannen en vrouwen, omdat het hogere DDK risico in mannen teniet wordt gedaan door hun kortere levensverwachting. De kosten en effecten van geïndividualiseerde screening waren marginaal beter dan die van uniforme screening in de hele bevolking. Met geïndividualiseerde screening werden echter meer levensjaren in de zwarte bevolking gewonnen, wat bijdraagt aan het terugdringen van de gezondheidsverschillen tussen blank en zwart.

Informeren van USPSTF aanbevelingen

In juli 2002 concludeerde de United States Preventive Services Task Force (USPSTF) dat er voldoende bewijs was om sterk aan te bevelen dat screening aangeboden zou moeten worden aan alle volwassenen van 50 jaar en ouder met een gemiddeld risico op DDK. De logistiek van screening, zoals het type test, het screeninterval, en de leeftijd om op te houden met screenen, werd echter niet geëvalueerd. Onlangst heeft de USPSTF de aanbevelingen voor DDK screening opnieuw beschouwd met een systematisch overzicht van het bewijs voor screentests. De USPSTF heeft ook gevraagd om een analyse om de verwachte uitkomsten van verschillende DDK screenstrategieën te voorspellen en met elkaar te vergelijken. In hoofdstuk 7 hebben we de MISCAN-Colon en SimCRC modellen gebruikt in een vergelijkende modelaanpak om gewonnen levensjaren te vergelijken van verschillende screenstrategieën in verhouding tot het gebruik van tests als proxy voor benodigde middelen. Op

leeftijd 50 beginnen met screenen was beter dan op leeftijd 60. Verlagen van de leeftijd om te stoppen met screenen van 85 naar 75 verminderde de gewonnen levensjaren met 1% tot 4%, terwijl het gebruik van colonoscopie afnam met 4% tot 15%. Uitgaande van gelijke opkomst, leverden 4 strategieën een vergelijkbaar aantal gewonnen levensjaren op: colonoscopie iedere 10 jaar, jaarlijkse Hemoccult SENSA of immunochemische FOBT en sigmoidoscopie iedere 5 jaar in combinatie met een FOBT elke 2-3 jaar. Hemoccult II en flexibele sigmoidoscopie alleen waren minder effectief.

Conclusies en aanbevelingen

- De duur van preklinische DDK is langer dan eerdere schattingen (bijna 7 jaar).
- De sensitiviteit van FOBT is hoger in het stadium waarin de kanker gediagnosticeerd zou worden zonder screening dan in eerdere stadia.
- Huidige beschikbare interventies hebben de potentie om DDK sterfte met 50% terug te dringen in de komende 20 jaar.
- DDK screening is zeer kosteneffectief vergeleken met geen screening. In de nabije toekomst kan het kostenbesparend worden.
- CTC screening moet niet aanbevolen worden als screentest voor de algemene bevolking, tenzij de kosten substantieel lager zijn dan die van colonoscopie.
- Geïndividualiseerde aanbevelingen zouden gezondheidsverschillen tussen blanken en zwarten terug kunnen dringen. De aanvaardbaarheid en uitvoerbaarheid van geïndividualiseerde aanbevelingen zouden daarom onderzocht moeten worden.
- Goede opties voor DDK screening zijn screening van leeftijd 50 tot leeftijd 75 met ofwel een jaarlijkse sensitieve FOBT, ofwel 10-jaarlijkse colonoscopie ofwel 5-jaarlijkse sigmoidoscopie in combinatie met FOBT elke 2-3 jaar.

Model appendix: The MISCAN-Colon microsimulation model

A.1 Introduction

This appendix contains an overview of the MISCAN-Colon model. Although all results in this thesis are based on the MISCAN-Colon model, the actual quantification of its input paramaters differ somewhat between the chapters, depending on the research question under investigation. This appendix first presents a general overview of the model and a listing of the parameters and assumptions. Where parameter values are the same in all chapters, this part also contains the quantification of model parameters. Parameters that differ between the individual chapters plus the reasons for this are presented in the final part of the appendix.

A.2 General model overview

The MISCAN-Colon model is a semi-Markov microsimulation model. The population is simulated individual by individual, and each person can evolve through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the MISCAN-Colon model generates durations in states and time of events. This improves model performance. With the assumption of exponential distribution of the duration in each state, this way of simulating leads to the same results as a Markov model with periodical transition probabilities. The advantage of the time-to-event approach is that durations in a certain state need not necessarily be a discrete value but can be continuous. MISCAN uses the Monte Carlo method to simulate all events in the program. Examples of possible events are birth and death of a person, adenoma incidence and transitions from one state of disease to another.

The basic structure of MISCAN-Colon is illustrated in Figure A.1. This figure clearly demonstrates that MISCAN-Colon consists of three parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is conceptually useful to consider them separately.

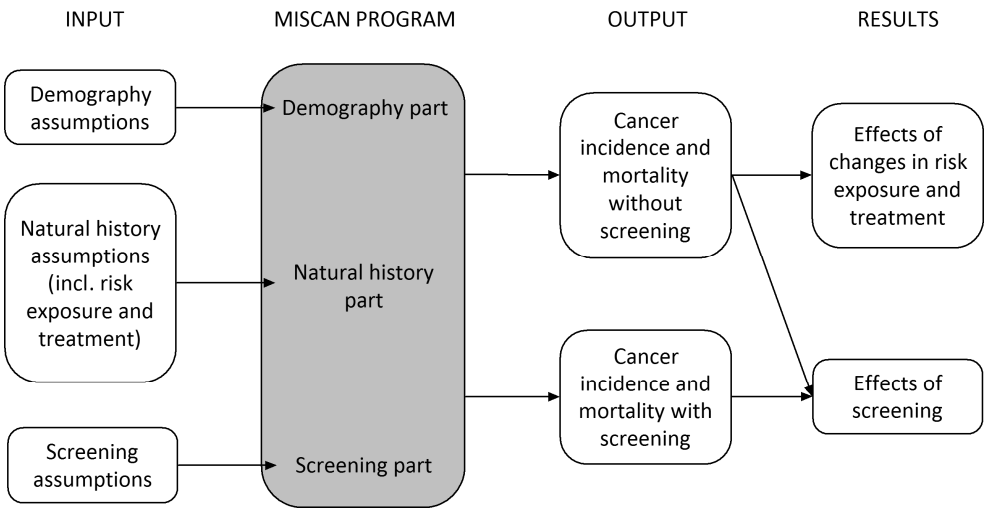

Figure A.1: Structure of MISCAN-Colon

Demography part

The demography part of the model simulates individual life histories without colorectal cancer (CRC) to form a population. For each person, a date of birth and a date of death of other causes than CRC are simulated. The distribution of births and deaths over calendar time can be adjusted to represent the population simulated. For example for the U.S., a population of white women will have higher death ages than a population of black men.

Natural history part

The natural history part of MISCAN-Colon simulates the development of CRC in the population. We assume all CRC develop according to the adenoma-carcinoma sequence of Morson[22] and Vogelstein[284] (Figure A.2). For each individual in the simulated population a personal risk index is generated. Subsequently, adenomas are generated in the population according to this personal risk index and an age specific incidence rate of adenomas. This results in no adenomas for most persons and one or more adenomas for others. The distribution of adenomas over the colorectum is simulated according to the observed distribution of CRC incidence. Each of the adenomas can independently develop into CRC. Adenomas can progress in size from small (1-5 mm) to medium (6-9 mm) to large (≥10 mm). Most adenomas will never develop into cancer (non-progressive adenomas), but some (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage there is a probability of the cancer being diagnosed because of symptoms. The survival after clinical diagnosis depends on the stage of the cancer.

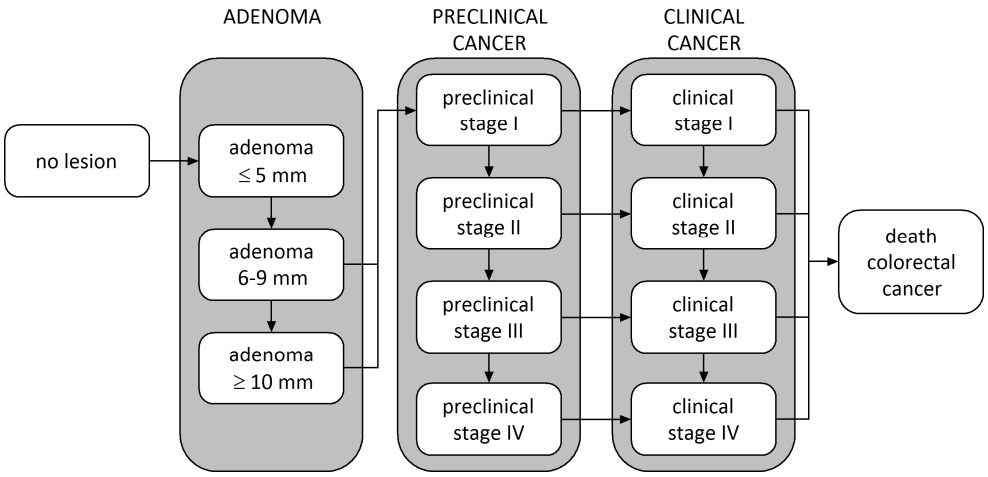

Figure A.2: Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for CRC. Adenomas are categorized by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age.

Screening part

Screening interrupts the development of CRC. With screening, adenomas may be detected and removed and cancers may be found, usually in an earlier stage than with clinical diagnosis. In this way screening prevents CRC incidence or CRC death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening. The effects of different screening policies can be compared by applying them to identical natural histories.

Integration of the three model components

For each individual, the demography part of the model simulates a time of birth and a time of death of other causes than CRC, creating a life history without CRC (top line in Figure A.3). Subsequently adenomas are simulated for that individual. For most individuals no adenomas are generated, for some one and for other multiple. In the example in Figure A.3, the person gets two adenomas (2nd and 3rd line in Figure A.3). The first adenoma arises at a certain age, grows into 6-9 mm and eventually becomes larger than 10 mm. However, this adenoma does not become cancer before the death from other causes than CRC of the person, either because it is a non-progressive adenoma, or because, although it is progressive, it does not make it to cancer before the end of life. The second adenoma is a progressive adenoma. 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. The life history without CRC and the development of the two adenomas in Figure A.3

together lead to the life history with CRC as depicted in the bottom line. Because this person dies from CRC before he dies from other causes, his death age is adjusted accordingly.

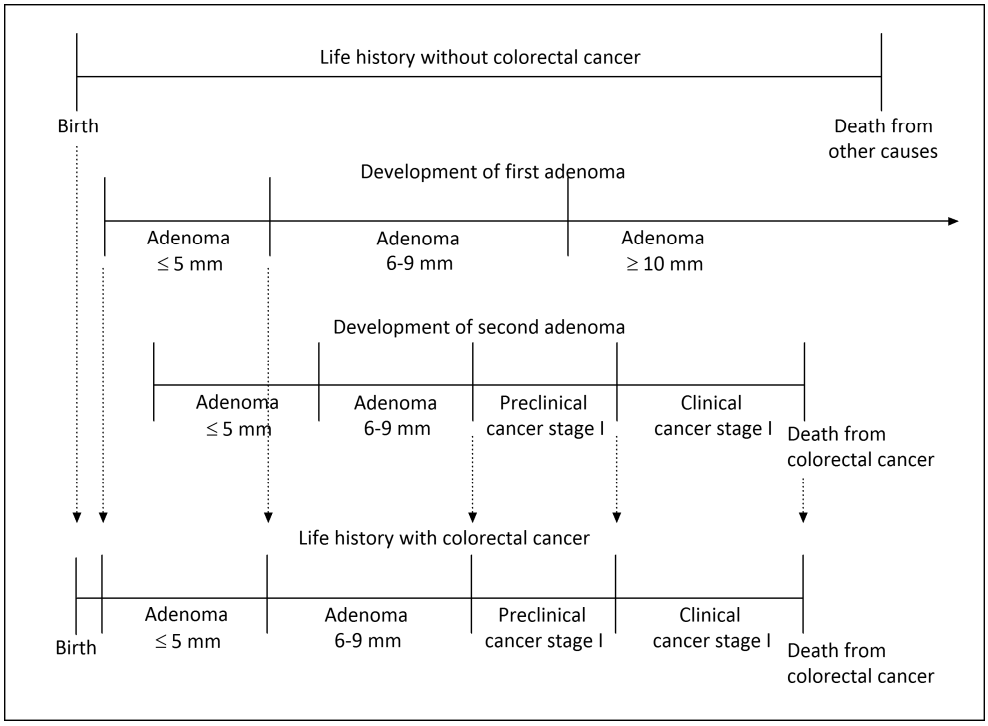

Figure A.3: Modeling natural history into life history.

After the life history of a person is adjusted for CRC, the history will now be adjusted for the effects of screening. The effect of screening on life history is explained in Figure A.4. The top line in this figure is the life history with CRC from Figure A.3. The development of the separate adenomas is repeated in the second and third line. In this picture there is one screening intervention. During the screening, in this example, both prevalent adenomas are detected and removed. This results in a life history with CRC and screening (bottom line). From the moment of screening the adenomas are removed and this individual becomes adenoma and carcinoma free. He does not develop cancer because the precursor lesion has been removed. Therefore the person dies at the simulated moment of death from other causes and the effect of screening is the difference in life-years in the situation without screening and the situation with screening. Of course many other possibilities could have occurred: 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 example this individual really benefited from the screening intervention.

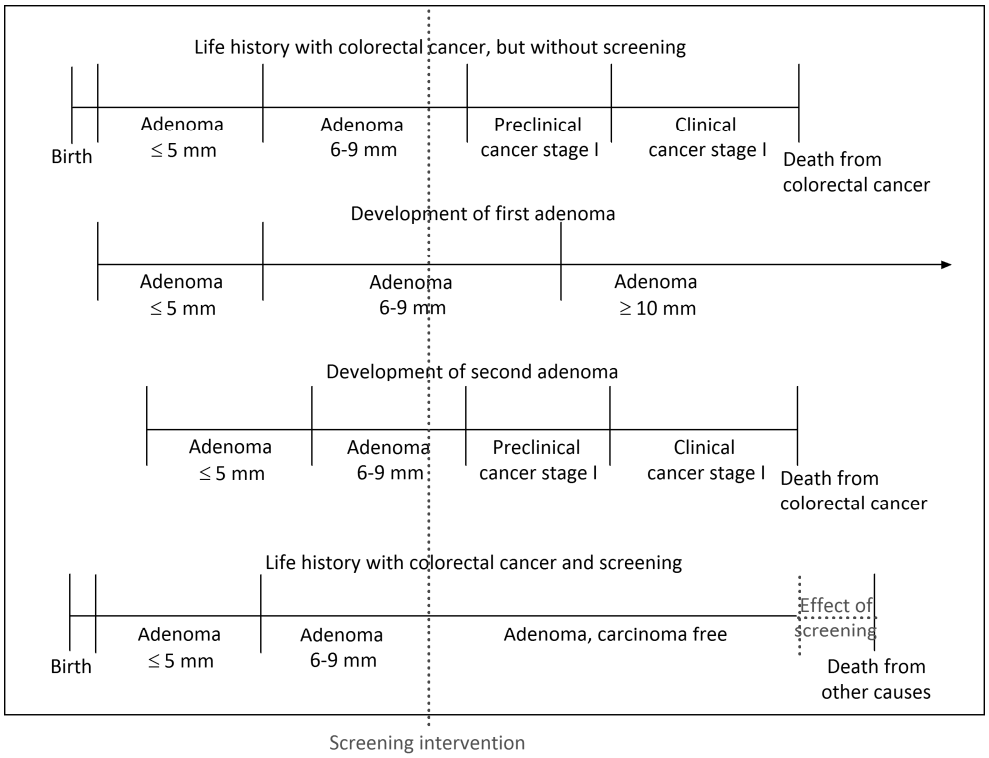

Figure A.4: Modeling screening into the life history.

A.3 Parameter overview and quantification of common parameters

Demography parameters

A population in MISCAN is built up from different birth cohorts. Each birth cohort has its own birth and life tables. Both depend on the population simulated and therefore differ between chapters.

Natural history parameters

The parameters for natural history model that could not be directly estimated from data or fit to reference data, were established based on expert opinion. At two expert meetings at the U.S. National Cancer Institute on June 5-7, 1996, and May 12-13, 1997, a model structure was devised in agreement with the currently accepted model of the adenoma-carcinoma sequence. It was assumed that all cancers are preceded by adenomas.

The expert panel agreed on an estimate of the average sojourn time (i.e., the duration between onset of a progressive adenoma and the clinical diagnosis of subsequent cancer) of 20 years. However, some adenomas do not make it to cancer in that time period, because people die of other

causes before the cancer could actually manifest. These are mainly the slower-developing adenomas with a longer duration than the average. The result is that the average duration of the adenomas that actually make it to diagnosed cancer is shorter, on average 10 years. The average duration of cancer in preclinical stages I-IV was 2 years, 1 year, 1.5 years, and 0.8 year, respectively, which resulted in a total average duration of 3.6 years because not every cancer reaches stage IV before clinical diagnosis. These sojourn times were based on the ratio between the stage-specific detection rate at first screening in fecal occult blood test trials and the background incidence, accounting for a 60% sensitivity of fecal occult blood test for all cancer stages.[28, 81] Only in chapter 2, the estimates for preclinical cancer sojourn time were different, because we there re-estimated fecal occult blood test (FOBT) sensitivity and preclinical cancer sojourn time based on the results of three large randomized controlled trials. All disease stage durations were governed by an exponential probability distribution. Durations in each of the invasive cancer stages as well as durations in the stages of the non-invasive adenomas were assumed to be 100% associated with each other, but the durations in invasive stages as a whole were independent of durations in non-invasive adenoma stages that preceded cancer. These assumptions resulted in an exponential distribution of the total duration of progressive non-invasive adenomas and of the total duration of preclinical cancer.

It was assumed that 30% of the cancers arise from adenomas of 6-9 mm and that 70% arise from larger adenomas. The preclinical incidence of progressive adenomas was chosen to reproduce CRC incidence by age, stage, and localization in the United States in the period before screening was performed (before 1980).[135] The size distribution of adenomas over all ages was assumed to be 56% for stages less than or equal to 5 mm, 24% for stages 6-9 mm, and 20% for stages greater than or equal to 10 mm. The preclinical incidence of non-progressive adenomas that will never grow into cancer was varied until the simulated prevalence of all adenomas was in agreement with data from autopsy studies. The autopsy studies used for this calibration differed from chapter to chapter. The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the observed site distribution of CRC.[135]

Table A.1 contains a summary of the model input values and its data-sources.

Table A.1: Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source
Regression of adenomas	No significant regression of adenomas	Expert opinion
Mean duration of development of progressive adenomas to clinical cancer	20 years	Expert opinion*
Mean duration of preclinical cancer†	3.6 years	Estimated from cancer detection rate at first screening and background cancer incidence in FOBT trials. [28, 81]
Mean duration of adenoma	16.4 years	20 years - 3.6 years
Percent of non-progressive adenomas that stay 6-9mm	50%	Fit to size distribution of adenomas in autopsy studies: [174-183] 1-5mm: 56% 6-9 mm: 24% ≥10 mm: 20%
Percent of non-progressive adenoma that become 10mm or larger	50%	Fit to size distribution of adenomas in autopsy studies: [174-183] 1-5mm: 56% 6-9 mm: 24% ≥10 mm: 20%
Percent of cancers that develops from 6-9mm adenoma and from ≥10 mm adenoma	30% of cancer develops from 6-9 mm, 70% from ≥10 mm	Expert opinion

* To be estimated from randomized controlled endoscopy trials, data not yet available.

† Re-estimated in chapter 2.

Screening parameters

The probability of adenoma and preclinical CRC detection is dependent on the sensitivity of the test for the lesion, the reach of the test and the location of the lesion. The actual parameters for reach and sensitivity of the tests differ from chapter to chapter. In case of detection and removal of an adenoma, it is assumed that the adenoma is prevented from growing into a cancer. In case of detection of a cancer, we assume the same stage specific survival for screen-detected as for clinically detected cancers.

A.4 Model differences from chapter to chapter

Demography parameters

Chapter 2

In chapter 2 the trial populations of the Funen, Nottingham and Minnesota populations were simulated. Although these populations will have slightly different life tables, we assumed the U.S. life table from 1989-1991 (National Center for Health Statistics http://www.cdc.gov/nchs/products/pubs/pubd/lftbls/life/1966.htm). The birth tables were chosen such that the age distribution at first screening of the simulated trial population met the observed age distribution at first screening.

Chapter 3

In chapter 3, we simulated the U.S. population from 1978 to 2020. The population size in this period by age was obtained from U.S. Census estimates and projections.[230] The life tables were based on the Berkeley life tables minus deaths from CRC.[285] Each five-year birth cohort had their own life table, equal to the life table associated with the middle birth year of the cohort. For future birth cohorts we assumed the same life table, as the latest one available.

Chapters 4 and 5

Chapters 4 and 5 concern a cohort analysis of the 50-year old population in 2008, meaning that we only simulated a cohort of individuals born in 1958. We used the Berkeley life table minus deaths from CRC for the population born in 1958.[285]

Chapters 6 and 7

Chapters 6 and 7 concern cohort analyses on a cohort of individuals born in 1967. The life tables were derived from the 2000 U.S. Life Table published by the National Center for Health Statistics

(http://www.cdc.gov/nchs/products/pubs/pubd/lftbls/life/1966.htm). These life tables include CRC mortality. We decided not to adjust the life tables because the percentage of CRC mortality in overall mortality is small and the data on CRC deaths by age, gender and race are sparse. For chapter 6, we used separate life tables by gender and race, while for chapter 7 we used a weighted average for the overall population.

Natural history parameters

This part explains the differences in the natural history quantification between the chapters. These differences are summarized at the end in Table A.2.

Chapter 2

The original MISCAN-Colon model developed by Loeve et al.[75-77] served as the basis for this analysis. This model was calibrated to 1978 SEER incidence by age, stage and localization, not corrected for second primary CRC.[135] The adenoma prevalence was calibrated to several autopsy and colonoscopy studies.[183, 197, 198, 227-229] Adjustments to the model for this particular analysis were adjustment of the CRC risk, stage distribution and survival to the control group estimates. Because estimation of the preclinical CRC sojourn time was one of the objectives of this study, this also differed from original.

Chapter 3

In chapter 3 the original MSCAN-Colon again served as the basis for the analysis.[75-77] Several adjustments were made to incorporate trends in risk factors and treatment. For each birth cohort, we estimated the relative risk of developing CRC compared to a hypothetical cohort without risk or protective factors for CRC by age. We assumed the relative risk for developing adenomas was equal to the relative risk for CRC 20 years earlier. The population of 1978 now consisted of different birth cohorts with different relative risks over their life. We calibrated the CRC incidence in the simulated 1978 population in the MISCAN-Colon model to the observed 1978 incidence. Changes in risk factor prevalence and thus relative risks over time resulted in different CRC incidence over time.

Chapters 4, 5 and 7

For chapters 4, 5 and 7, we used improved CRC incidence and adenoma prevalence data to calibrate the model to. Instead of using just one year of CRC incidence data, we used 1975-1979 incidence data from SEER that were corrected for second and later primary CRC.[135] This made the data more robust and in better concordance with the simulated data where we also only model first CRC. Furthermore, adenoma prevalence data were based on a wider collection of autopsy studies from approximately the same period.[174-183] Because the countries and years in which the autopsy studies were performed differed with respect to CRC incidence, we adjusted the adenoma prevalence data

with the incidence ratio between U.S. CRC incidence in 1975-1979 and the incidence of the respective country and years the autopsy study was from. We used Globocan data to obtain the incidence ratios.[3] Survival data were updated to the latest period available and were made dependent on age.

Chapter 6

For this analysis, we used the same approach as we did for chapter 2. We used the original MISCAN-Colon model calibrated to the SEER 1978 CRC incidence[135] and data from colonoscopy and autopsy studies.[183, 197, 198, 227-229] This model was now adjusted for each population subgroup to obtain 1997-2001 models for white and black men and women. We assumed that all difference in CRC incidence between the 1978 general population model and the 1997-2001 race- and gender specific models was caused by differences in adenoma incidence. We therefore adjusted the age-specific incidence of both progressive and non-progressive adenomas so that the CRC incidence by gender, race, age, stage and location from 1997-2001 was reproduced. The anatomic site distribution of both progressive and non-progressive adenomas and thus of preclinical and clinical cancers is assumed to be equal to the site distribution of CRC in the United States in 1997-2001.[135] The stage-specific survival after the clinical diagnosis of CRC is taken from the Surveillance, Epidemiology, and End Results registry data from 1987 through 2001.[135]

Table A.2: Difference in natural history quantification of the MISCAN-Colon model by chapter

Model parameter	All chapters	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7
Distribution of risk for adenomas over the general population	Fit to multiplicity distribution of adenomas in autopsy studies	Autopsy study [183]	Autopsy study [183]	Autopsy studies [174-183]	Autopsy studies [174-183]	Autopsy study [183]	Autopsy studies [174-183]
Adenoma incidence in general population	Fit to adenoma prevalence in colonoscopy and autopsy studies	Colonoscopy and autopsy studies [183, 197, 198, 227-229]	Colonoscopy and autopsy studies [183, 197, 198, 227-229]	Autopsy studies [174-183]	Autopsy studies [174-183]	Colonoscopy and autopsy studies [183, 197, 198, 227-229]	Autopsy studies [174-183]
Probability that a new adenoma is progressive	Fit to adenoma prevalence in colonoscopy and autopsy studies and to cancer incidence in SEER	Colonoscopy and autopsy studies [183, 197, 198, 227-229] SEER 1978.[135] Adjusted to CRC level in control groups	Colonoscopy and autopsy studies [183, 197, 198, 227-229] SEER 1978.[135] Different risk level by birth cohort based on risk factor trends	Autopsy studies [174-183] SEER 1975-1979,[135] corrected for second and later primaries	Autopsy studies [174-183] SEER 1975-1979,[135] corrected for second and later primaries	Colonoscopy and autopsy studies [183, 197, 198, 227-229] SEER 1978.[135] Adjusted to CRC level in 1997-2001 by race and gender	Autopsy studies [174-183] SEER 1975-1979,[135] corrected for second and later primaries
Localization distribution of adenomas and cancer	Directly estimated from SEER	SEER 1978 [135]	SEER 1978 [135]	SEER 1975-1979,[135] corrected for second and later primaries	SEER 1975-1979,[135] corrected for second and later primaries	SEER 1997-2001 [135]	SEER 1975-1979,[135] corrected for second and later primaries

Table A2 continued

Model parameter	All chapters	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7
Stage distribution	Fit to stage distribution in SEER	SEER 1978 [135]	SEER 1978 [135]	SEER 1975-1979,[135] corrected for second and later primaries	SEER 1975-1979,[135] corrected for second and later primaries	SEER 1997-2001 [135]	SEER 1975-1979,[135] corrected for second and later primaries
Survival	Directly estimated from SEER (except survival in Minnesota study in chapter 2)	Control group survival (Minnesota) SEER 1975-1993 [135] (Nottingham and Funen)	SEER 1975-1979.[135] Adjusted to more recent estimates based on utilization patterns and effectiveness of chemotherapy	SEER 1998-2003 [135]	SEER 1990-1994, SEER 1998-2003. [135]	SEER 1997-2001 [135]	SEER 1998-2003 [135]

Screen parameters

Table A.3 shows a summary of differences in sources for CRC test characteristics including complication rates in the different chapters.

Chapter 2

In chapter 2 obtaining an estimate of the sensitivity of Hemoccult II was one of the objectives. The estimates for colonoscopy sensitivity were based on two back-to-back colonoscopy studies[117, 118] and the cecal intubation rate was based on results from the Kaiser Permanente sigmoidoscopy screening study.[218] Complications with colonoscopy were not modeled.

Chapter 3

Chapter 3 used the same values for colonoscopy as chapter 2, and assumed that the colonoscopy sensitivities also applied to sigmoidoscopy within the reach of the sigmoidoscope, except for diminutive adenomas where sensitivity was slightly lower. Reach for sigmoidoscopy was also based on results of the Kaiser Permanente sigmoidoscopy screening study.[218] The sensitivity and specificity of Hemoccult II were based on the results of the European randomized controlled FOBT trials.[80, 81] Complications with colonoscopy were not modeled.

Chapters 4 to 7

In chapters 4 to 7 test characteristics of all tests were based on the test characteristics used in our analysis on the cost-effectiveness of stool DNA.[42] In that analysis, test characteristics of the fecal occult blood tests Hemoccult II, Hemoccult SENSA and fecal immunochemical test (FIT) were based on a literature review.[42] The sensitivity estimate for Hemoccult II was lower than used in chapter 3 (40% instead of 60%). For colonoscopy and sigmoidoscopy, sensitivity estimates within reach were based on a review of back-to-back colonoscopy studies.[53] As a result only colonoscopy sensitivity for diminutive adenomas was changed from 80% to 75% compared to chapters 2 and 3. Risks of complications with colonoscopy were based on those reported in organized screening programs[187-189] and general practice colonoscopies.[58, 222]

Table A.3: Differences in sources for screening test characteristics in the MISCAN-Colon model by chapter

Test characteristic	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7
Sensitivity Hemoccult II	Re-estimated	Gyrd-Hansen, 1997 [81]	-	Literature review [42]	-	Literature review [42]
Sensitivity SENSA	-	-	-	Literature review [42]	-	Literature review [42]
Sensitivity FIT	-	-	-	Literature review [42]	-	Literature review [42]
Sensitivity sigmoidoscopy	-	Loeve, 2000;[77] Hixson, 1991;[117] and Rex, 1997.[118]	-	Van Rijn, 2006 [53]	-	Van Rijn, 2006 [53]
Sensitivity colonoscopy	Hixson, 1991;[117] and Rex, 1997.[118]	Hixson, 1991;[117] and Rex, 1997.[118]	Van Rijn, 2006 [53]	Van Rijn, 2006 [53]	Van Rijn, 2006 [53]	Van Rijn, 2006 [53]
Sensitivity CTC	-	-	Mulhall, 2005 [50]	-	-	-
Reach sigmoidoscopy	-	Levin, 1999 [218]	-	Levin, 1999 [218]	-	Levin, 1999 [218]
Cecal intubation rate with colonoscopy	Levin, 1999 [218]	Levin, 1999 [218]	General practice [219, 220] and guidelines [58]	General practice [219, 220] and guidelines [58]	General practice [219, 220] and guidelines [58]	General practice [219, 220] and guidelines [58]
Complication rate with colonoscopy	Not modeled	Not modeled	Organized screening programs[187-189] and general practice [58, 222]	Organized screening programs[187-189] and general practice [58, 222]	Organized screening programs[187-189] and general practice [58, 222]	Not modeled
Fatal complication rate with colonoscopy	Not modeled	Not modeled	Prospective endoscopy study [190]	Prospective endoscopy study [190]	Prospective endoscopy study [190]	Prospective endoscopy study [190]

SENSA = Hemoccult SENSA; FIT = fecal immunochemical test; CTC = CT Colonography.

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Dankwoord

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PhD portfolio summary
Summary of PhD training and teaching activities

Name PhD student: Iris Lansdorp-Vogelaar
Erasmus MC Department: Public Health

PhD period: 2003-2009
Promotor: Prof. dr. J.D.F. Habbema
Supervisor: Dr. M. van Ballegooijen

1. PhD training	Year	Workload
Research skills		
Erasmus Summer Programme, Erasmus MC Rotterdam		
- Bayesian analysis	2004	0.7 ECTS
- Topics in meta-analysis	2005	0.7 ECTS
- Survival analysis	2005	1.4 ECTS
Nihes, Erasmus MC, Rotterdam:		
- Planning and evaluation of screening	2004	1.4 ECTS
American Gastroenterological Association		
- Methodologies in healthcare outcomes in gastroenterology	2004	16 hours
Joint Statistical Meetings		
- Computational statistics: Methods for Monte Carlo integration and optimization	2006	8 hours
ENAR spring meeting		
- Statistical analysis of cost-effectiveness data	2008	3 hours
Presentations		
National Cancer Institute, Cancer Intervention and Surveillance Modeling Network (CISNET), Bethesda Maryland		
- Validation of FOBT studies	2004	10 hours
- Base Case II: Comparing the impact of screening on life histories	2004	10 hours
- Base Case III: Suggestions for runs and outputs	2004	10 hours
- Validation of FOBT studies - progress	2005	10 hours
- Benefit of customizing colorectal cancer screening - An exploration with colonoscopy screening	2006	10 hours
- Screening with virtual colonoscopy - What to do with small polyps?	2006	10 hours
- Model evidence and approach for regression of adenomas	2007	10 hours
- MiscRisk: Carcinogenesis model in MISCAN - Features and possibilities	2007	10 hours
- Lessons learned in the CISNET-Colon group	2008	10 hours
- Survival after screen detection	2008	10 hours
Methodologies in Healthcare Outcomes in Gastroenterology		
- Colorectal cancer mortality: Can we reach the Healthy People 2010 goal?	2004	20 hours
Nederlands Congres Volksgezondheid, Rotterdam		
- Dikkedarmkanker: primaire, secundaire of tertiaire preventie?	2005	20 hours
Joint Statistical Meetings, Seattle		
- Screening with virtual colonoscopy - Should small polyps be referred for removal?	2006	20 hours

1. PhD training	Year	Workload
Presentation continued		
European Guidelines for Quality Assurance in Colorectal Cancer Screening, Lyon and Budapest		
- European CRC screening quality assurance guidelines - Chapter 1: Introduction	2007, 2008	20 hours
Northern Ireland Health Economics Workshop , Belfast		
- Population-based colorectal cancer modeling	2007	20 hours
ENAR spring meeting, Arlington Virginia		
- The methodology and advantages of comparative modeling in microsimulation analyses	2008	20 hours
Workshop on future directions in CRC screening in Europe, Vienna		
- Evidence for the (cost-)effectiveness of CRC screening	2008	20 hours
International conferences		
European School of Oncology - Colorectal Cancer Conference, London	2005	16 hours
Joint Statistical Meetings, Seattle, Washington, D.C.	2006	40 hours
ENAR spring meeting, Arlington, Virginia	2008	32 hours
EU CRC Screening Guidelines Network Meeting, Budapest	2008	16 hours
Seminars and workshops		
Attending seminars of the department of Public Health	2003-2008	100 hours
Secundaire preventie van gastro-enterologische tumoren	2005	4 hours
Northern Ireland Health Economics Workshop , Belfast	2007	8 hours
Workshop on future directions in CRC screening in Europe, Vienna	2008	8 hours
Didactic skills		
Erasmus MC, Rotterdam		
- Startbijeenkomst van onderwijsthema 4.2 'De populatie als patiënt'	2008	1 hour
- Docententraining voor vaardigheidsonderwijs	2008	2 hours

2. Teaching activities	Year	Workload
Lecturing		
Nihes course 'Planning and evaluation of screening', Erasmus MC Rotterdam:		
- MISCAN: a simulation program for cancer screening analysis	2004-2007	16 hours
Curriculum medical students, 4th year, Erasmus MC Rotterdam:		
- Theme 4.2: The population as a patient	2008	60 hours
Supervising Master's theses		
- Andrew Yong: Multistage carcinogenesis models for adenoma prevalence and cancer incidence	2008-2009	50 hours

Curriculum vitae van Iris Lansdorp-Vogelaar

Iris Lansdorp-Vogelaar werd geboren op 4 december 1978 in Leidschendam. In 1997 behaalde zij haar gymnasium diploma aan het Stedelijk Gymnasium in Leiden. In datzelfde jaar startte zij met de studie Econometrie aan de Erasmus Universiteit Rotterdam. Zij volgde hierbij de duale afstudeerrichting, waarbij de wetenschappelijke studie wordt aangevuld met een jaar werkervaring. Deze periode heeft zij ingevuld bij het toenmalige NEI bv, waarbij ze onderzoek deed op het gebied van arbeid en sociaal beleid. In 2002 rondde zij haar studie Econometrie af met als specialisatie 'Logistiek'. Haar scriptie betrof onderzoek naar modellen voor arbeidsmarktvoorspellingen voor verschillende sectoren van de Nederlandse economie. Na haar afstuderen, heeft zij nog een jaar bij NEI, inmiddels Ecorys, onderzoek gedaan op het gebied van arbeidsmarktvoorspellingen en efficientie van non-profit instellingen.

Vanaf augustus 2003 tot heden is zij in dienst van de afdeling Maatschappelijke Gezondheidszorg van Erasmus MC, Universitair Medisch Centrum Rotterdam. Hier doet zij onderzoek naar de kosten en effecten van dikkedarmkanker screening met behulp van het MISCAN-Colon microsimulatie model. Daarnaast is zij auteur van een hoofdstuk in de European Guidelines for Quality Assurance in Colorectal Cancer Screening. Na haar promotie blijft zij verbonden aan de afdeling Maatschappelijke Gezondheidszorg.