Effects and costs of colorectal cancer screening and follow-up after polypectomy

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This thesis is partly realized due to the financial support of the Department of Public Health, Erasmus MC, University Medical Center Rotterdam and ORTEC bv.

Effects and costs of colorectal cancer screening and follow-up after polypectomy / Loeve, Franka
Thesis Erasmus MC, University Medical Center Rotterdam – With summary in English and Dutch

Cover design: Peter Vogelaar, Studio PV, Rotterdam, peter.vogelaar@uitdekunst.com
Printed by: PrintPartners Ipskamp, Enschede

ISBN 90-9017256-4

Effects and costs of colorectal cancer screening and follow-up after polypectomy

Effecten en kosten van dikke-darmkankerscreening en follow-up na poliepectomie

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam op gezag van de

rector magnificus

Prof.dr. ir J.H. van Bemmel

en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op

woensdag 22 oktober 2003 om 11.45 uur

door

Franka Loeve

geboren te Rotterdam

Promotiecommissie

Promotor:	Prof.dr.ir. J.D.F. Habbema
Overige leden:	Prof.dr. J.H. Kleibeuker Prof.dr. E.J. Kuipers Prof.dr. F.F.H. Rutten
Copromotor:	Dr. R. Boer

Contents

Publications

Chapter 2-7 are based on the following publications.

Chapter 2

F. Loeve, R. Boer, G.J. van Oortmarssen, M. van Ballegooijen and J.D.F. Habbema (1999). The MISCAN-COLON Simulation Model for the Evaluation of Colorectal Cancer Screening. Comput Biomed Res 32(1): 13-33.
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Chapter 3

F. Loeve, R. Boer, G.J. van Oortmarssen, M. van Ballegooijen and J.D.F. Habbema (2001). Impact of systematic false-negative test results on the performance of faecal occult blood screening. Eur J Cancer 37(7): 912-7.
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Chapter 4

F. Loeve, M.L. Brown, R. Boer, M. van Ballegooijen, G.J. van Oortmarssen and J.D.F. Habbema (2000). Endoscopic Colorectal Cancer Screening: a Cost-Saving Analysis. J Natl Cancer Inst 92(7): 557-63.
F. Loeve, M.L. Brown, R. Boer and J.D.F. Habbema (2000). Re: Improving the Cost-Effectiveness of Colorectal Cancer Screening. J Natl Cancer Inst 92(20): 1691-2.
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Chapter 5

F. Loeve, R. Boer, A.G. Zauber, M. van Ballegooijen, G.J. van Oortmarssen, S.J. Winawer and J.D.F. Habbema. National Polyp Study Data: Evidence for Regression of Adenomas. (submitted for publication)

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Chapter 7

F. Loeve, M. van Ballegooijen, R. Boer, E.J. Kuipers and J.D.F. Habbema. Colorectal Cancer Risk in Adenoma Patients: a Nation-Wide Study. (submitted for publication)

1

Introduction

Colorectal cancer as a public health problem

Colorectal cancer is a major public health problem. In most Western countries, colorectal cancer is the third most common cancer in men, next to lung and prostate cancer. It is the second commonest cancer in women, after breast cancer. This thesis focuses on colorectal cancer in the Netherlands and the United States.

In 1997, approximately 8,500 new cases of colorectal cancer were diagnosed in the Netherlands and more than 4,000 individuals died of the disease [Visser 2001]. The estimated number of new colorectal cancer cases for the United States in 2002 is 148,300 and 56,600 deaths from colorectal cancer are expected [American Cancer Society 2002]. Figure 1.1 shows the colorectal cancer incidence and mortality in 1997 in the Netherlands [Visser 2001]. The age-specific incidence increases from 12 per 100,000 in males and 11 in females at age 40-44 years to 490 in males and 332 in females at age 80-84 years. Figure 1.2 shows the cumulative colorectal cancer risk and mortality in the Netherlands

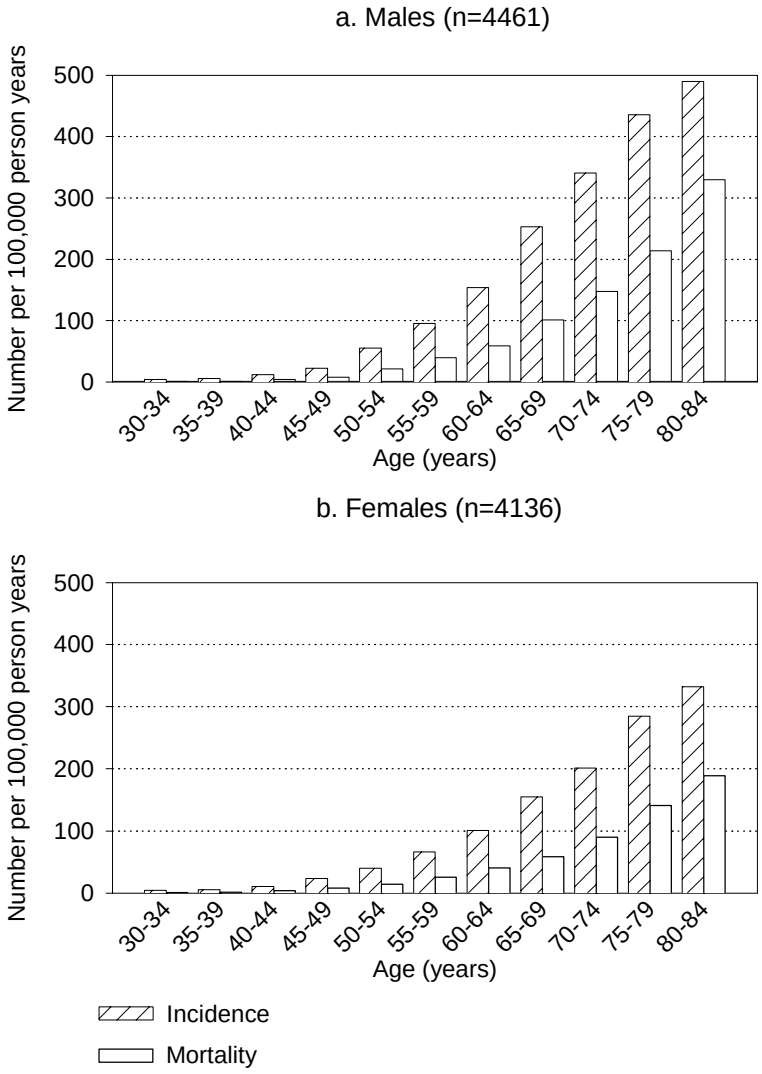

Figure 1.1 Colorectal cancer incidence and mortality in the Netherlands in 1997.

according to age [Visser 2001]. The lifetime colorectal cancer risk in the Netherlands is 5.5% for men and 5.4% for women [Visser 1997]. The incidence of colorectal cancer in the United States is 10-20% higher than in the Netherlands [Coebergh 1995]. The lifetime colorectal cancer risk in the United States is 6.0% for men and 5.6% for women [Feuer 1999]. The cumulative mortality risk at the age of 75 years is 1.9% for men and 1.2% for women in the Netherlands [Visser 2001]. According to our own calculations, colorectal cancer decreases the life expectancy of a 50-years old person by 4.5 months. Around 95% of all new cases of colorectal cancer are diagnosed in people with no known predisposing factors for the disease. The remainder occur in patients with Hereditary Non-Polyposis Colorectal Cancer (HNPCC), patients with Familial Adenomatous Polyposis (FAP), and patients with Inflammatory Bowel Disease (IBD) [Lynch 1993, Burt 1996b, Gezondheidsraad 2001, Samowitz 2001]. Many cases of colorectal cancer diagnosed in individuals under the age of 50 concern such high-risk patients, while the majority of

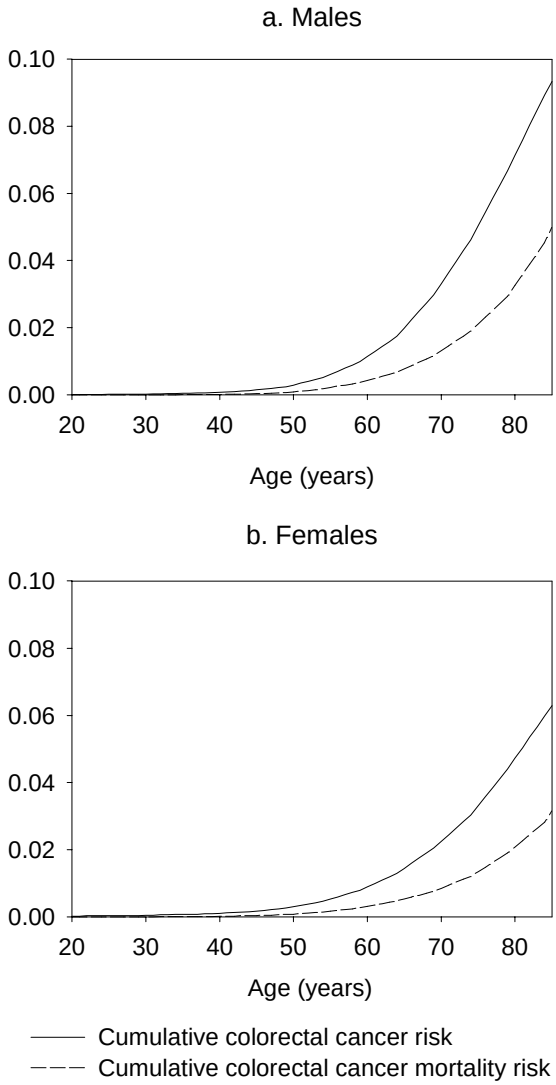

Figure 1.2 Cumulative colorectal cancer risk and colorectal cancer mortality risk in the Netherlands in 1997.

colorectal cancer cases diagnosed in individuals aged 50 and up are sporadic, i.e., they occur in patients with no known increased risk for colorectal cancer. As the number of known gene mutations causing hereditary colorectal cancer continues to expand over the coming years, the incidence in patients with a known genetic predisposition for colorectal cancer will similarly increase.

The treatment and survival following colorectal cancer diagnosis depend on the stage at which the cancer is detected. The classification according to the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) distinguishes 4 stages in colorectal cancer, largely corresponding to the previously used Dukes' stages, that reflect the extent to which the cancer has extended from its origin through the wall of the bowel, to regional lymph nodes, and to distant sites. AJCC/UICC stage I or Dukes' A cancer involves the inner wall of the colon or rectum. An AJCC/UICC stage II or Dukes' B cancer has spread outside the colon or rectum to nearby tissue, but not to the lymph nodes. An AJCC/UICC stage III or Dukes' C cancer has spread to nearby lymph nodes, but not to other parts of the body. An AJCC/UICC stage IV or Dukes' D cancer has spread to other parts of the body, such as the liver or lungs [National Cancer Institute 2002]. In the Netherlands, 19% of the colorectal cancer cases diagnosed between 1989-1992 related to Dukes' stage A cancers, 34% to Dukes' stage B, 22% to Dukes' stage C and 17% to Dukes' stage D tumors. No stage was known in 8% of the cases [Damhuis 1996]. In the United States, 19% of the colorectal cancer cases between 1973 and 1994 were diagnosed as AJCC/UICC stage I cancers, 30% as stage II, 20% as stage III and 21% as stage IV tumors [National Cancer Institute 1997].

If the colorectal tumor is resectable, the cancer is treated by curative surgery resulting in a hemicolectomy or total colectomy. Rectum cancer patients may be treated pre-operatively by radiotherapy. Most stage III colon cancer patients are treated by adjuvant chemotherapy after surgery. Chemotherapy is not standard for stage III rectum cancer patients, but some stage III rectum cancer patients are treated with radiotherapy. Stage IV colon and rectum cancer patients are usually treated by palliative surgery of the primary tumor and palliative chemotherapy. Stage IV rectum patients may be treated by palliative radiotherapy if the tumor bleeds or causes pain. After the initial treatment, colorectal cancer patients are regularly monitored by colonoscopy and blood tests [Integraal Kankercentrum Noord-Nederland 2000, Landelijke tumorwerkgroep gastro-intestinale tumoren 2000]. Almost all colorectal cancer deaths occur within 5 years after diagnosis [Berrino 1995, Winawer 1997]. The survival rate in the United States is similar to that in the Netherlands. Around 90% of patients diagnosed with stage I/Dukes' stage A are still alive after 5 years, while the 5 year survival rate for patients diagnosed with stage IV/Dukes' stage D is only 5% [Coebergh 1995, National Cancer Institute 1997]. Survival in the Netherlands after colorectal cancer diagnosis has improved slightly over time, which is partly attributable to a decrease in short-term mortality after surgery [Coebergh 1995].

Natural history

The colorectal tract or large bowel consists of several parts: rectum, rectosigmoid, sigmoid, descending colon, splenic flexure, transverse colon, hepatic flexure, ascending colon, and cecum. The distal part or left side of the bowel consists of the rectum, the rectosigmoid, sigmoid, and the descending colon. In some definitions, the splenic flexure is also part of the distal bowel. The remainder is the proximal part or right side of the bowel. It is generally thought that colorectal cancer develops from adenomas, the so-called adenoma-carcinoma sequence [Muto 1975, Morson 1984]. Figure 1.3 shows the adenoma-carcinoma sequence schematically. At time point A, the bowel tissue transforms from normal tissue into an adenomatous polyp: an adenoma. Adenomas can grow anywhere in the bowel. 40-60% of the adenomas grows in the distal part of the bowel. Figure 1.4 shows the adenoma prevalence according to age estimated from autopsy data [Koretz 1993]. Some 30%-50% of all aging individuals has adenomas. According to a study of 518 autopsies in the United States, the mean number of adenomas in individuals with at least one adenoma is 2.3 in individuals aged <60 years, 2.4 in individuals aged 60-74 years, and 3.3 in individuals aged over 75 years [Rickert 1979]. Most adenomas are polypoid, but flat adenomas have also been reported [Hart 1998, Rembacken 2000]. Usually, adenomas do not cause symptoms and most adenomas will not develop into cancer. In some cases, adenomas can even disappear again ("regression of adenomas"). This is shown in Figure 1.3 by arrow B. Non-adenomatous lesions may also develop in the large bowel, such as hyperplastic polyps and lipomas. These lesions are generally thought not to be precursors of cancer.

The onset of malignancy in an adenoma is indicated by time point C in Figure 1.3. At that point, malignant cancer cells are detectable in the adenoma. It is likely to take many years for an adenoma to grow into cancer [Muto 1975], although this period varies from case to case. Some adenomas may progress very quickly into colorectal cancer. Initially, the cancer will be preclinical; i.e., it will not yet cause symptoms. At a certain point, the cancer will cause symptoms such as blood in stool, weight loss or abdominal pain. Following clinical diagnosis of the cancer due to symptoms at time point D, the cancer is referred to as "clinical cancer". Observation of the "preclinical period", or time between the onset and the diagnosis of colorectal cancer due to symptoms, is obviously impossible. Koretz estimated the length of this preclinical period by comparing the number of malignant lesions detected by screening sigmoidoscopy or at surgical polypectomy with the annual incidence of colorectal cancer. According to his estimate, an

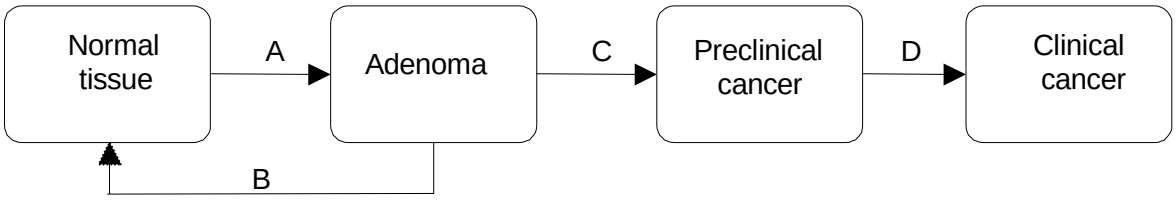

Figure 1.3 The adenoma-carcinoma sequence. A, onset of adenoma; B, regression of adenoma; C, onset of preclinical colorectal cancer; D, Diagnosis of colorectal cancer.

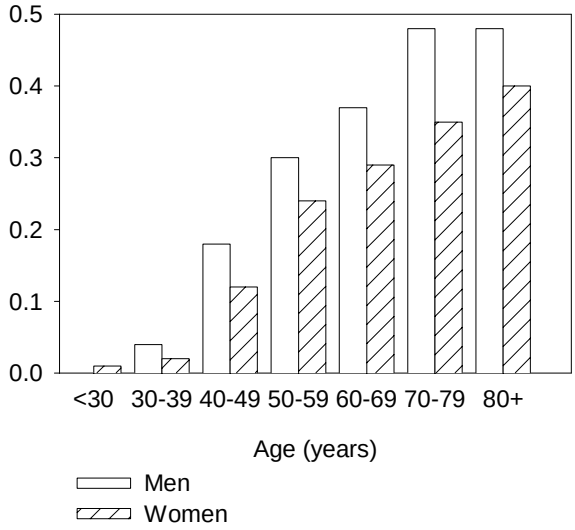

Figure 1.4 Estimated adenoma prevalence based on autopsy data [Koretz 1993].

average of 4.8 years is needed for malignant polyps to become clinically apparent cancer [Koretz 1993]. The length of the preclinical period is 4.5-5 years according to an analysis of the screen-detection rate at the first fecal occult blood test (FOBT) screening and the interval cancer rate in Calvados, France [Launoy 1997]. An analysis of screen-detection rates and interval cancer rates in four rounds of the Funen FOBT study resulted in an estimate of 2.1 years for the preclinical period [Gyrd-Hansen 1997].

Primary prevention

Primary prevention of colorectal cancer aims to prevent colorectal cancer by changing lifestyle factors in the general population, such as smoking, obesity and diet. The relation between lifestyle factors and colorectal cancer has been addressed in many studies. Most trials focussed on the effect of lifestyle on incidence and development of adenomas and not on colorectal cancer incidence or mortality. The Polyp Prevention Study, a clinical trial of antioxidant vitamins, reported no adenoma incidence reduction in the intervention group [Greenberg 1994]. Two trials (the Polyp Prevention Trial and the Wheat Bran Fiber Trial) found that a high fiber diet did not significantly reduce adenoma recurrence after 3-4 years [Alberts 2000, Schatzkin 2000]. Neither study was intended to study the effect of diet on colorectal cancer incidence, but more cancers were diagnosed in the intervention group than in the control group. However, the study periods were short (4 years on average), and the Wheat Bran Fiber Trial focussed on intervention through administering fiber bars instead of offering dietary counseling to the intervention group. The Polyp Prevention Trial was the only study in which the intervention group received dietary counseling. Observational studies find that the risk for colorectal cancer is lower among populations with a high intake of fruits and vegetables [Byers 2000]. Possibly, therefore, diet does not affect adenoma incidence, but does reduce colorectal cancer incidence.

A clinical trial has reported that calcium supplementation is associated with a significant – though moderate – decrease in adenoma recurrence [Baron 1999].

Furthermore, a trial studied the effect of aspirin intake on the incidence of adenomas in patients with a recent history of adenomas [Baron 2003]. The authors concluded that daily intake of 81 mg aspirin has a moderate preventive effect on adenoma incidence in the large bowel. However, no preventive effect was seen in patients who received 325 mg aspirin. Another trial studied the effect of daily intake of 325 mg aspirin on incidence of adenomas in patients with a history of colorectal cancer [Sandler 2003]. The study concluded that daily use of aspirin is associated with a significant reduction in the adenoma incidence in patients with a history of colorectal cancer. Case-control studies and observational studies suggest an effect of aspirin intake on the incidence of colorectal cancer [Garcia Rodriguez 2000], but this has not yet been confirmed by randomized trials.

Screening for disease

Secondary prevention focuses on early detection of a disease to reduce disease-specific morbidity or mortality. Secondary prevention of colorectal cancer mortality by screening in the general population has the potential to save lives by early detection of colorectal cancer or even prevention of colorectal cancer by removal of adenomas. A screening test should distinguish individuals who are likely to have the disease from individuals who are not likely to have the disease. An effective and acceptable screening program is a program that leads to mortality reduction and does not cause harm to the participants. In most Western countries, screening for breast cancer and for cervical cancer is performed. There are several possible screening tests for colorectal cancer. Fecal Occult Blood Tests (FOBT), sigmoidoscopy, colonoscopy, and Barium Enema are introduced below. Other recent screening tests such as DNA markers in stool and virtual colonoscopy are described in Chapter 8.

Fecal Occult Blood Test

Fecal occult blood tests detect blood in stool from bleeding asymptomatic colorectal cancers or large adenomas. Several types of FOBT test are available. Most common is the guaiac FOBT test, for example the Hemoccult II test (SmithKline Diagnostics). The screenee can perform this test at home. The screenee receives an FOBT kit and smears feces onto slides on 1-3 consecutive days. In most screening programs, the screenees are asked to restrict their diet, for example by not consuming red meat during those days. The slides are processed in a laboratory. Screenees with a positive test are invited for diagnostic colonoscopy. The FOBT test primarily aims at detecting preclinical colorectal cancer. The slides may be rehydrated with water during processing, which increases the probability to detect preclinical cancer. The sensitivity of unrehydrated guaiac FOBT for preclinical cancer, i.e., the probability that the test is positive in patients with preclinical cancer, was estimated by performing unrehydrated FOBT and colonoscopy in 554 patients referred for colonoscopy. In these patients, 16 cancers were detected by FOBT and colonoscopy and the sensitivity of the FOBT test for cancer was 86% [Greenberg 2000]. The sensitivity of unrehydrated guaiac FOBT was also estimated by analyzing the results

of the Funen FOBT trial and was estimated to be 62% [Gyrd-Hansen 1997]. The sensitivity of unrehydrated guaiac FOBT for adenomas is low and increases from 2-5% for adenomas <5mm to 10-30% for adenomas sized ≥10mm. In a recent study, unrehydrated guaiac FOBT was positive in 1% of 76 patients with an adenoma <5mm and in 21% of 39 patients with adenomas ≥10mm [Greenberg 2000]. In a study by Ahlquist *et al.*, unrehydrated guaiac FOBT was positive in 6% of 223 patients with adenomas larger than 10mm [Ahlquist 1993]. This means that the majority of the adenomas detected by unrehydrated guaiac FOBT are chance findings. The specificity of the unrehydrated guaiac FOBT test, i.e., the probability that the test is negative in a person without preclinical cancer or adenomas, is 95-98%. In the Greenberg study, 94% of the patients with no adenomas or cancer had a negative unrehydrated FOBT test [Greenberg 2000], while 95% of the patients in the Ahlquist study with no adenomas or cancer had a negative test [Ahlquist 1993]. Rehydration of the test improves the sensitivity of the test, but decreases its specificity. In the Minnesota Colon Cancer Control Study, rehydration of the test increased the sensitivity of the test for cancer from 81% to 92%, but decreased the specificity of FOBT from 98% to 90% [Mandel 1993]. In another study, the sensitivity of rehydrated guaiac FOBT was tested in 2885 individuals screened by colonoscopy [Lieberman 2001]. The sensitivity of FOBT for tubular adenomas <10mm was 7%, the sensitivity for tubular adenomas ≥10mm was 17.5% and the sensitivity for colorectal cancer was 50%. The specificity of the test was 93.8%.

The sensitivity of FOBT at the first screening round of a screening program or trial is probably higher than the sensitivity at a repeat screening, because at a repeat screening most preclinical cancers will have developed recently. Most of these cancers are in an early stage and it is likely that FOBT is less sensitive for early cancer stages. A decrease in sensitivity of FOBT for colorectal cancer at repeat screening has indeed been reported by the Nottingham FOBT study. The sensitivity of FOBT for cancer was estimated from the study by dividing the number of screen detected cancers by the number of screen detected plus interval cancers within two years following a negative screening. The sensitivity of FOBT at the first screening round was estimated to be 70%, while the sensitivity of FOBT at repeat screening decreased from 58% at screening round 2 to 48% at screening round 5, with a mean sensitivity of 52% [Moss 1999]. The sensitivity of FOBT at repeat screening may also be lower because some adenomas and cancers that were missed at previous screening rounds never bleed and will never be detected by FOBT. These lesions will cause systematic negative FOBT results.

Three randomized controlled trials have demonstrated that FOBT screening reduces colorectal cancer mortality [Towler 1998]. The trials in Funen and in Nottingham that studied biennial unrehydrated guaiac FOBT screening found a mortality reduction in the screened group of 18% and 15% respectively compared with a control group receiving usual care [Hardcastle 1996, Kronborg 1996]. The Minnesota trial, that used both rehydrated and unrehydrated FOBT, found a mortality reduction of 18% in the biennially screened group and 33% in the annually screened group compared with the control group [Mandel 1999]. Meanwhile, new immunochemical FOBT tests have been developed that

are more sensitive for cancer. An advantage of the immunochemical tests is that dietary restrictions are not necessary [Rozen 1997].

Because FOBT aims for detection of preclinical cancer, and the average duration of preclinical cancer is a few years, it has been offered every year or every two years, starting around the age of 50 years.

Endoscopic tests

Two other screening tests- sigmoidoscopy and colonoscopy- are both endoscopic tests that require the bowel to be cleaned in advance. The colorectal tract is visualized by insertion of a small video-endoscope through the anus. If polyps are detected in the tract, they can be removed immediately. Sigmoidoscopy visualizes the distal part of the bowel, which contains 40-60% of the adenomas and colorectal cancers [Winawer 1997]. Sigmoidoscopy does not require sedation, while colonoscopy visualizes the entire bowel and requires sedation. Usually, if lesions are detected during sigmoidoscopy, they are biopsied and the tissue is sent to pathology. If the tissue is adenomatous, a colonoscopy is scheduled. The colonoscopy visualizes the complete colorectal tract and all detected lesions are removed. Sigmoidoscopies and colonoscopies are usually performed by gastroenterologists, although trained nurses can also perform sigmoidoscopies without polypectomy. Trained nurses should not, however, perform colonoscopies, as these involve sedation and a higher risk of complication.

Both colonoscopy and sigmoidoscopy are accompanied by a small risk of complications caused by either perforation of the bowel or by the sedation. The major complication of sigmoidoscopy, perforation of the bowel, occurs in between 1 and 2 cases per 10,000 procedures, and slightly more frequently if biopsy or polypectomy is performed during sigmoidoscopy [Winawer 1997]. The UK Flexible Sigmoidoscopy Screening Trial reported only 1 perforation during more than 40,000 sigmoidoscopic procedures [UK Flexible Sigmoidoscopy Screening Trial Investigators 2002]. Complications due to bleeding are not seen in colonoscopies without polypectomy, although 0.5-7 perforations and 5-10 other minor complications are reported per 1000 procedures. Therapeutic colonoscopy with polypectomy causes 0.5-2 major bleedings, 1-10 perforations and 5-10 other minor complications per 1000 procedures [Winawer 1997]. The UK Flexible Sigmoidoscopy Screening Trial reported 4 perforations during 2377 colonoscopic procedures, i.e., 1.7 per 1000. All perforations in the UK trial followed polypectomy [UK Flexible Sigmoidoscopy Screening Trial Investigators 2002]. The VA Cooperative Study reported no perforations during 3196 screening colonoscopies [Nelson 2002]. During approximately 5 per 1000 colonoscopic procedures, patients experience clinically significant respiratory depression [Winawer 1997]. Mortality due to colonoscopy occurs in 0.5-3 per 10,000 colonoscopic procedures without polypectomy and in 0.5-10 per 10,000 colonoscopic procedures with polypectomy [Kwaliteitsinstituut voor de gezondheidszorg CBO 2002]. Mortality due to sigmoidoscopy has not been reported. Endoscopy imposes a larger burden on the screenee compared with FOBT due to the invasive character of the test and the complication risk.

Colonoscopy and sigmoidoscopy aim to detect both adenomas and preclinical cancer. The removal of adenomas reduces the incidence of colorectal cancer. The sensitivity of colonoscopy for adenomas has been estimated to be 76% in a study in which two colonoscopic examinations were performed on the same day in patients [Rex 1997b]. Estimated sensitivity was 73% for adenomas ≤5mm, 87% for adenomas 6-9mm, and 94% for adenomas ≥10mm. These are upper limits for the sensitivity of colonoscopy, because some adenomas may have been missed by both examinations. The sensitivity of colonoscopy for cancer has been estimated by reviewing medical records of 2193 colorectal cancer cases and was approximately 95% [Rex 1997c]. In a screening program with repeat endoscopic screening, the sensitivity of endoscopy at repeat screening will probably be smaller than the sensitivity at first screening, because most adenomas and preclinical cancers will have developed recently. The average size of the adenomas (and cancer) will therefore be smaller at repeat screening. Some lesions removed at endoscopy will be non-adenomatous, such as hyperplastic polyps. The specificity of colonoscopy, i.e., the probability that the test is negative in a person without preclinical cancer or adenomas is probably 80-90%.

To date, no direct evidence for the effectiveness of endoscopy screening is yet available from large randomized controlled trials. Because endoscopic screening mainly aims to detect and remove adenomas, the effectiveness of endoscopic screening depends to a large extent on the natural history of the adenoma-carcinoma sequence. A very small randomized controlled trial, the Telemark study, found a 80% colorectal cancer incidence reduction in the group screened with sigmoidoscopy compared with a control group with no screening (95% confidence interval, 3%-95%) [Thiis-Evensen 1999]. However, in this trial the all-cause mortality in the control group was significantly higher than in the screen group, which may indicate that the randomization did not result in comparable groups. The Kaiser Permanente Multiphasic evaluation study found a significant reduction in colorectal cancer mortality among participants randomized to undergo an annual health check-up including sigmoidoscopy [Selby 1988]. However, the exposure to sigmoidoscopy screening was similar in the study and control group (30% versus 25% examined at least once between 1965 and 1974) and there was no difference in polyp detection between the groups. Three case-control studies suggest that sigmoidoscopy screening reduces colorectal cancer mortality considerably [Newcomb 1992, Selby 1992, Muller 1995a] and another case-control study suggest that sigmoidoscopy screening reduces colorectal cancer incidence [Muller 1995b]. A prospective, non-randomized study in health professionals found that screening endoscopy reduced colorectal cancer incidence by 58% (95% confidence interval, 36%-96%) and reduced colorectal cancer mortality by 56% (95% confidence interval, 32%-91%) [Kavanagh 1998]. A non-randomized controlled trial in families with Hereditary Nonpolyposis Colorectal Cancer (HNPCC), found a significant reduction in colorectal cancer incidence of 62% in the group screened every 3 years with colonoscopy or barium enema and sigmoidoscopy (95% confidence interval, 17%-83%) [Järvinen 1995, Järvinen 2000]. However, observational studies, such as case-control studies or non-randomized follow-up studies may lead to biased outcomes [Weiss 1996, Connor 2000].

It could be argued that the 33% mortality reduction in the annually screened group during the first 13 follow-up years of the Minnesota FOBT study is also caused by diagnostic colonoscopy after a positive FOBT test [Mandel 1993]. Because diagnostic colonoscopy is an essential part of the screening strategy in the FOBT trials, the fact that the FOBT trials reported a significant reduction in colorectal cancer mortality supports the notion that colonoscopic screening reduces mortality. It is possible that the mortality reduction in the Minnesota FOBT study was not only caused by early detection of cancer, but also by removal of adenomas at diagnostic colonoscopy. The positivity rate in the trial increased from 2% to 15% during the trial. Approximately 83% of the patients with positive tests complied with colonoscopy and the proportion of the individuals in the annually screened group who had had at least one colonoscopy was 31% after nine years of screening activity [Ederer 1997]. The theory that part of the mortality reduction is caused by adenoma removal is supported by the significant reduction of colorectal cancer incidence in the screened groups compared with the control group [Mandel 2000]. The cumulative incidence ratio compared with the control group in an 18-year follow-up period was 0.80 (95% confidence interval, 0.70-0.90) in the annually screened group and 0.83 (95% confidence interval, 0.73-0.94) in the biennially screened group.

The effect of colonoscopy can also be studied by comparing the cancer incidence in adenoma patients who had had adenomas removed during colonoscopy to that in adenoma patients in whom adenomas were not removed. The National Polyp Study (NPS) and Funen study population consisted of adenoma patients in whom adenomas were removed and who were surveilled regularly with colonoscopy. The Stryker study reported cancer incidence in patients with adenomas ≥10mm in whom adenomas were not removed but were surveilled via radiological examinations in the Mayo clinic [Stryker 1987]. Compared with the cancer incidence in the Stryker study, the cancer incidence in patients with adenomas ≥10mm was reduced to 7% (95% confidence interval, 2%-22%) in the NPS [Winawer 1993a] and to 57% (95% confidence interval, 27%-104%) in the Funen study [Jørgensen 1993].

Because sigmoidoscopy and colonoscopy aim to detect not only colorectal cancer but also adenomas and preclinical cancer, the interval between two screening tests can be larger than for FOBT. Screening intervals of 5 or 10 years, starting at the age of 50 years, have been recommended and some gastroenterologists even suggest a once-only sigmoidoscopy or colonoscopy at the age of 50-60 years.

Barium Enema examination

The barium enema examination is a radiological examination during which the complete colon is visualized. This test also requires the bowel to be cleaned before the examination. A barium enema examination imposes a small radiation risk on the screenee. The radiation dose is approximately 1-2 times the radiation dose of screening mammography [Winawer 1997]. The burden of the test for the screenee is probably similar to the burden of endoscopy. Complications due to perforation occur in 1-40 per 10,000 barium enema procedures [de Zwart 2001]. Barium enema can detect large adenomas as well as

preclinical cancer. The sensitivity of the test for adenomas has been reported by the investigators of the National Polyp Study [Winawer 2000] as being 32% for adenomas ≤5mm, 53% for adenomas 6-10mm, and 48% for adenomas ≥10mm. In this study, a barium enema was performed in adenoma patients prior to a surveillance colonoscopy. Barium enemas have also been found to have a sensitivity for adenomas of 70% or higher in various other studies [Williams 1974, Fork 1981, Brewster 1984, Irvine 1988, Saito 1989, Steine 1993, Kewenter 1995, Glick 1998, de Zwart 2001] that, however, were not performed in average-risk patients, but in patients with a positive FOBT test, or in patients referred for colonoscopy or barium enema due to symptoms. Furthermore, in some studies, the barium enema was not followed by a colonoscopy, but by sigmoidoscopy or a second barium enema [Brewster 1984, Saito 1989, Kewenter 1995]. The sensitivity of barium enema for cancer has been estimated by reviewing the medical records of 719 colorectal cancer patients whose initial diagnosis was made by barium enema. Barium enema detected the cancer in 596 patients and missed the cancer in 123, which meant a sensitivity of 83% [Rex 1997c]. In a retrospective study of 571 colon cancer patients who had had a barium enema during the diagnostic process, 91% of the colorectal cancers were correctly diagnosed; the cancer was missed in 7% of the cases and the barium enema was unsuccessful in 2% of the patients [Strom 1999]. Specificity estimates range from 90% to 98% [de Zwart 2001].

A larger screening interval can be applied in barium enema screening than when using FOBT, as barium enema detects not only cancer but also large adenomas. However, the interval selected should be shorter than for sigmoidoscopy and colonoscopy, due to the inability to detect small adenomas. A screening interval of 5 years has been suggested [Smith 2002, Winawer 2003]. The effectiveness of barium enema screening has not been studied in large randomized trials. Barium enema seems less appropriate for screening than endoscopic tests, because the sensitivity for adenomas and cancer is lower than endoscopy and it imposes a radiation risk.

Population screening

Since the results of the randomized controlled trials of FOBT screening have become available, several guidelines for colorectal cancer screening in the average-risk population have been published [The European Group for Colorectal Cancer Screening 1999, Smith 2002, Winawer 2003].

The European Group for Colorectal Cancer has concluded that there is sufficient evidence that FOBT screening reduces colorectal cancer mortality [The European Group for Colorectal Cancer Screening 1999]. The group recommends implementation of repeat FOBT screening for asymptomatic individuals aged ≥ 50 years with colonoscopic follow-up after a positive test. No guidelines for screening have yet been published in the Netherlands. The Health Council of the Netherlands recently advised the Minister of Health that a number of research questions should be answered prior to implementation of screening in the Netherlands [Gezondheidsraad 2001]. No data on screening activity in the Netherlands are available, but the screening rates are very low.

In most United States guidelines, various screening strategies are recommended for individuals aged ≥50 years, and the patient can choose according to his or her preference. Recommended screening strategies in the United States are: FOBT screening (yearly), flexible sigmoidoscopy every 5 years, yearly FOBT combined with sigmoidoscopy screening every 5 years, double contrast barium enema every 5 years and colonoscopy every 10 years [Smith 2002, Winawer 2003]. The 1999 Behavioral Risk Factor Surveillance System (BRFSS), a telephone survey, contains data on the use of FOBT and sigmoidoscopy/colonoscopy in the United States. Overall, 21% of the respondents aged ≥50 years reported to have had FOBT during the preceding year and 34% reported having had a sigmoidoscopy/colonoscopy during the preceding 5 years [Behavioral Risk Factor Surveillance System 1999, Centers for Disease Control and Prevention 2001].

Screening high-risk populations

Members of Hereditary Non-Polyposis Colorectal Cancer (HNPCC) families, Familial Adenomatous Polyposis patients (FAP), and patients with Inflammatory Bowel Disease (IBD) have a more than average risk for colorectal cancer. For these patients, colonoscopic surveillance or even total colectomy is recommended.

HNPCC family members have a genetic pre-disposition for colorectal cancer. A common standard to identify HNPCC families are the Amsterdam criteria that were established by the International Collaborative Group (ICG) meeting in Amsterdam in 1990. All criteria should be satisfied: 1) three or more relatives should be diagnosed with colorectal cancer, one of whom is a first-degree relative of the other two, 2) at least two generations should be affected, 3) one cancer case should be diagnosed below age 50, 4) familial adenomatous polyposis should be excluded and 5) tumors should be verified by pathological examination [Vasen 1991]. In 1999, the first criterium was revised to include other HNPCC-associated cancers: colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis [Vasen 1999b].

HNPCC is generally caused by a mutation of mismatch repair genes [Burt 1996b]. The lifetime risk to develop colorectal cancer in carriers of MLH1 and MSH2 mutations is 60-70%, calculated by survival analysis using clinical and pathologic data from 138 families with HNPCC [Vasen 2001]. For HNPCC patients with a genetic mutation or applying to the Amsterdam criteria, colonoscopic surveillance is recommended [Burt 1996a, Winawer 1997]. Individuals with a family history of colorectal cancer who do not meet the Amsterdam criteria are also believed to be at high risk for colorectal cancer. The relative risk to develop colorectal cancer for first-degree family members of colorectal cancer patients is approximately 4 compared with family members of individuals without colorectal cancer [Vasen 1999a]. This relative risk strongly depends on the age of colorectal cancer diagnosis. In first-degree family members of patients who were diagnosed at older age, the relative risk is lower than 4. The American Gastroenterological Association recommends genetic testing for HNPCC to first-degree relatives of persons with a known inherited mismatch repair gene mutation. It should also be offered when the family mutation is not known, but one of the following criteria is met: 1) individuals with

cancer in families that meet the Amsterdam criteria, 2) individuals with 2 HNPCC-related cancers, 3) individuals with colorectal cancer and a first-degree relative with an HNPCC-related cancer or colorectal adenoma, one of the cancers diagnosed at age <45 years, and the adenoma diagnosed < 40 years [Winawer 2003]. Colonoscopic screening is one of the options for individuals in the Netherlands with one first-degree relative with colorectal cancer diagnosed before the age of 45 and for all individuals with two first-degree relatives with colorectal cancer [Vasen 1999a]. The estimated relative risk in these individuals is 4-6 compared to individuals with no relatives with colorectal cancer. A trial is ongoing in the Netherlands to investigate the effect of surveillance on the incidence of high-risk adenomas in individuals with a first-degree relative diagnosed with colorectal cancer before the age 50 and in individuals with two first-degree relatives with colorectal cancer [Gezondheidsraad: Commissie WBO 2000].

FAP patients have hundreds or thousands of adenomas in the bowel and the first adenomas develop between age 10 and 30. FAP arises from mutations of the adenomatous polyposis coli (APC) gene on chromosome 5 and is an autosomal dominant inherited disease [Burt 1996b]. Almost 100% of these patients will develop colorectal cancer if the colon is not removed [Burt 1996b, Winawer 1997] and total colectomy should be performed [American Society for Gastrointestinal Endoscopy 2000, Winawer 2003]. Genetic counseling and mutation-analysis should be considered in first-degree relatives of these patients. If relatives test positive, they should be screened by colonoscopy or flexible sigmoidoscopy until they develop polyps. At that point, colectomy should be considered [Burt 1996a, Winawer 2003].

Colonoscopic surveillance is also recommended for patients with a history of Inflammatory Bowel Disease, such as ulcerative colitis and Crohn's disease, because they are at increased risk for colorectal cancer. The relative risk is estimated to be 6 compared with the general population [Ekbom 1990].

Surveillance of adenoma patients

If adenomas are diagnosed in an individual, the adenomas should be removed completely by polypectomy, because adenomas may develop into cancer. Stryker retrospectively followed 226 patients who had large polyps that were not removed and who were surveilled by radiographic examination. It was estimated that the colorectal cancer risk in large polyps was 8% at 10 years, climbing to 24% at 20 years after the initial diagnosis [Stryker 1987]. Furthermore, the risk of developing cancer at another site than the index polyp was estimated to be four times higher than in the general population [Otchy 1996]. Therefore, adenoma patients are believed to be at high risk for new adenomas and/or cancer and colonoscopic surveillance of these patients is recommended. Surveillance is considered an essential aspect in a screening strategy, as endoscopic, and, to a lesser extent, FOBT screening, can detect patients with adenomas. Hence the required endoscopy capacity depends not only on the screening strategy, but also on the surveillance policy of patients in whom adenomas are detected.

Surveillance guidelines for Dutch adenoma patients were first published in 1988 [Snel 1988]. These guidelines stated that the first surveillance colonoscopy should be performed within a year after the initial polypectomy. The follow-up interval should be either 3 or 5 years, depending on the number of adenomas found. Since then, the National Polyp Study has reported their results. This study randomized 1418 patients in whom adenomas had been removed at colonoscopy. One group was surveilled with colonoscopy at 3 and 6 years since initial adenoma removal. The other group was surveilled with colonoscopy at 1, 3, and 6 years since initial adenoma removal. Patients were followed for 5.9 years on average. The study investigators concluded that surveillance colonoscopy 1 year after initial polypectomy was not needed and that the first surveillance colonoscopy after initial colonoscopy could be scheduled after 3 years [Winawer 1993b]. The Dutch guidelines were revised in 2002 [Nagengast 2001, Kwaliteitsinstituut voor de gezondheidszorg CBO 2002] and now recommend that patients with one or two adenomas undergo a surveillance colonoscopy 6 years after the initial polypectomy. If three or more adenomas are found at initial colonoscopy, patients should undergo a surveillance colonoscopy 3 years after the initial polypectomy. If fewer than three adenomas are detected at surveillance colonoscopy, the next surveillance colonoscopy should be performed 6 years later. If at that time three or more adenomas are detected, the next surveillance colonoscopy should be performed 3 years later. Surveillance can cease at age 65 in patients with cumulative 1 adenoma, and at age 75 in patients with cumulative 2 adenomas. Surveillance in patients with cumulative 3 or more adenomas should continue as long as the patient's health permits. If no adenomas are found in 3 consecutive surveillance colonoscopies, surveillance can stop.

The optimal follow-up interval depends on the cancer incidence in the first years after polypectomy. If the cancer incidence in the first years after polypectomy is low compared with incidence in the general population, the follow-up interval between initial polypectomy and first surveillance interval can be long. But if colonoscopy frequently misses progressive adenomas and new potentially malignant adenomas develop rapidly, the cancer incidence in the first years after polypectomy will be high and the interval between initial polypectomy and the first surveillance interval must therefore be small.

Principles for screening for disease

In 1968, Wilson and Jungner defined 10 principles for screening for a particular disease [Wilson 1968]:

1. The disease should be an important public health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the disease, including development from latent to declared disease, should be adequately understood.

8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding, including diagnosis and treatment of patients diagnosed should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a “once and for all” project.

In Chapter 8, these principles will be applied to FOBT and endoscopic screening in the Netherlands. These principles are useful to indicate which diseases are potential targets for screening and which screening tests are appropriate. They are not intended to be absolute criteria to decide whether or not screening should be performed, as some screening programs that do not meet all these principles may still be worthwhile. A good example is the “hielprik” (heel stick) in the Netherlands. More than 99% of the 200,000 babies born in the Netherlands each year are screened by the heel stick for two metabolic diseases: congenital hypothyroidism (CHT) and phenylketonurea (PKU). Both diseases are minor public health problems because they are rare: the heel stick detects approximately 60-70 CHT patients and 10-15 PKU patients each year. The CHT and PKU screening program is still worthwhile because the heel stick is easy to perform, the sensitivity and specificity of the screening tests are high and the tests for these diseases are combined.

At present, it is commonly thought that it is not strictly necessary for the natural history to be well understood (principle 7), if there is evidence that screening reduces disease-specific mortality. Ideally, this is proved in a randomized controlled trial. For example, cervical cancer screening is performed in many Western countries even though the natural history of cervical cancer is not clear and it is unknown which cervical lesions will progress or regress. Evidence that cervical cancer screening reduces mortality is based on case-control studies and studies that compare regions or periods with and without screening.

If it is agreed that a disease is a potential target for screening, the following issue to consider is whether the health effects of screening outweigh the costs of screening and which screening strategy will be offered or recommended to the population. Screening strategies can differ as to the ages at which screening is offered, the screening test itself, and the diagnostic test following a positive screening test. An important element in this decision-making process is a cost-effectiveness analysis in which the costs and effects of several screening strategies are compared. It may even be concluded from the cost-effectiveness analysis that the costs of screening are too high compared to the health effects gained. This is related to principle 9: whether or not the costs of screening are worthwhile compared to other interventions.

Cost-effectiveness analysis

In a cost-effectiveness analysis, the costs and effects of alternative screening strategies are calculated and represented by a cost-effectiveness ratio [Gold 1996]. Effects are health outcomes, for screening strategies usually expressed in lifeyears gained, quality-adjusted lifeyears gained, or deaths prevented. Costs of a screening strategy consist of extra costs of

screening, diagnostic follow-up, treatment of complications, and surveillance tests minus savings in treatment costs. The incremental cost-effectiveness ratio of a screening strategy compared with a less intensive screening strategy is the ratio between the extra costs of the intensive strategy and the extra lifeyears gained by the intensive strategy. A screening strategy is considered efficient if there is no alternative strategy that results in more lifeyears gained with equal or less costs. In an empirical study or trial, the costs and effects of a screening strategy can be studied directly. However, in order to calculate costs and effects of alternative screening strategies that have not been studied in observational studies, it is common to use a model-based approach to extrapolate the findings in randomized controlled trials and observational studies.

It is important to consider the negative effects of screening when deciding on a screening strategy. Examples of negative health effects of screening are over-diagnosis, i.e., detection of disease that would never have been diagnosed without screening, complications of screening and diagnostic follow-up, false-positive test results, and the burden of the screening test itself. These negative effects of screening are not incorporated in the cost-effectiveness ratio if the effects are expressed in lifeyears gained and should be considered additionally. If the effects are expressed in quality-adjusted lifeyears (QALY) gained, the negative effects are included in the measure of effect. A quality-adjusted life year is a measure of health outcome that assigns a weight, ranging from 0 to 1, to each period of time, corresponding to the health-related quality of life during that period. A weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death. These weights are then aggregated across time periods. By using this health measure, negative health effects of screening can be incorporated into the cost-effectiveness ratio. In order to gain insight into the cost-effectiveness ratio, it is worthwhile to consider intermediate results on the costs and effects.

The MISCAN-COLON model

Mathematical models are useful to test hypotheses about the epidemiology, the natural history of disease, characteristics of screening tests, and the effect of screen-detection on prognosis. Models can also be used to predict the (cost-) effectiveness of screening strategies. In this thesis, the MISCAN-COLON model is presented and used to estimate costs and effects of colorectal cancer screening and surveillance of adenoma patients. The original MISCAN (MIcrosimulation SCreening ANalysis) model [Habbema 1984], which is being used for breast and cervical cancer screening evaluation, was not developed to simulate the natural history of colorectal cancer. Therefore, the original model was re-written to a MISCAN-COLON model in 1996. New aspects in the MISCAN-COLON model include possibilities for the simulation of more than one lesion per person, the simulation of a specific anatomical site at which the lesion develops within the colon, and the simulation of surveillance examinations after detection of a polyp.

The MISCAN-COLON model simulates a large number of fictitious individual life histories. In each life history, several colorectal lesions can emerge. Next, screening for colorectal cancer is simulated, which will change some of the life histories. The

aggregated changes in life histories constitute the effectiveness of the screening. The effect of alternative screening strategies can be compared by applying them to identical life histories. The assumptions in the Miscan model consist of assumptions about deep parameters and assumptions about situation parameters. The deep parameters describe the natural history, diagnosis and treatment of colorectal cancer and the improvement in prognosis due to screen-detection. Examples of deep parameters are the duration distribution of adenomas and colorectal cancer, the sensitivity and specificity of the screening test and the impact of early detection and treatment on a patients' prognosis. The deep parameters cannot be directly observed, but can be estimated by experts or from screening trial data and other relevant data, such as autopsy studies. Situation parameters describe the population and the considered screening strategy. Examples of situation parameters are the life table, the cancer incidence and stage distribution in the situation without screening, the screening strategy, the surveillance strategy of adenoma patients, and the compliance with screening. The computer program gives detailed output on colorectal cancer incidence, mortality, and the effects of screening, see Table 1.1. The output can be used for cost calculations by multiplying the number of tests and colorectal cancer cases with the unit costs of a test or treatment.

The deep model parameters on natural history, screen test characteristics and survival are initially quantified by literature review and/or expert opinion. Figure 1.5 shows the process of parameter optimization in order to narrow down the uncertainty about deep model parameters. In this process, model results are compared with observed results in an empirical study. First, a study-specific model quantification is constructed by combining the initial quantification of the deep parameters with the situation parameters that describe the empirical study, such as background incidence in the population, and the screening strategy. The study cohort is then simulated and the simulated results are

Table 1.1 Main output of the MISCAN-COLON computer program. All output by age and calendar year.

Output of MISCAN-COLON computer program
Number of invitations
Number of attenders of first screening resp. first screening tests
Number of attenders of repeat screening, resp. repeat screening tests
Results of first screening tests (positive / negative)
Results of repeat screening tests (positive / negative)
Results of diagnostic tests after positive screening test (positive for adenoma / positive for cancer / negative)
Results of surveillance tests (positive for adenoma / positive for cancer / negative)
Number of colorectal cancer cases diagnosed due to symptoms
Number of lifeyears
Number of lifeyears gained due to screening
Number of colorectal cancer deaths*
Number of deaths due to other causes

* Both with and without screening. The difference is the effect of screening.

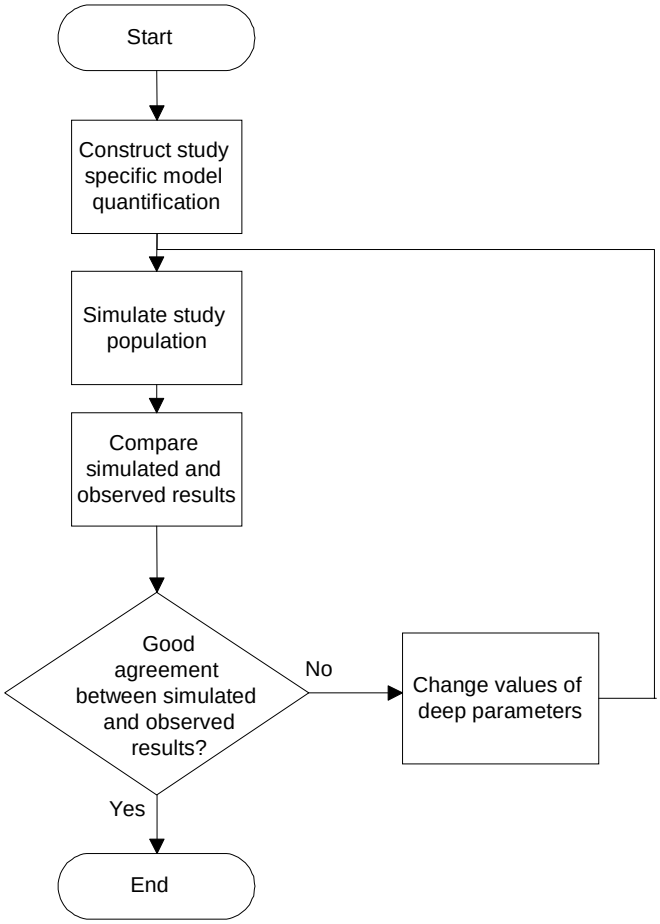

Figure 1.5 Parameter optimization with the MISCAN-COLON model: finding deep model parameters that fit the results of an empirical study by testing simulated results against observed results.

compared with the results observed in the study. If the simulated results do not agree with the observed results, the deep parameters are adjusted in order to achieve better agreement. A MISCAN run is performed using the new model quantification and the simulated results are compared again with observed results. The parameter optimization procedure is stopped if good-fitting deep parameter values are found or if no further improvement in deep parameter values is expected. This parameter optimization process can be performed by hand or by an automated optimization procedure. By repeating the parameter optimization procedure with a different initial quantification of the deep parameters, several sets of deep parameter values may be obtained that all explain the observed study results equally well.

Next, the model can be used to perform projections on the costs and effects of screening strategies. The deep parameter values that resulted from the parameter optimization procedure are combined with situation parameter values that describe the considered screening strategy. The simulated results of the screened population can be combined with unit cost estimates in order to predict the costs and cost-effectiveness of the screening strategy. If these simulations are performed for several screening strategies, the costs and effects of the strategies can be compared and this will result in a list of

efficient screening strategies. The model can also be used for other purposes such as estimating the personnel capacity needed for a screening program and estimating the health effects of a screening program over time, which is important for evaluation of ongoing screening programs.

The MISCAN model for cervical cancer screening has been used to estimate cost-effectiveness of cervical cancer screening in The Netherlands [Habbema 1985, Koopmanschap 1990a, Koopmanschap 1990b, van Ballegooijen 1992, van den Akker-van Marle 2002] and to explore the potential value of HPV testing for cervical cancer screening [van Ballegooijen 1997, Cuzick 1999]. For breast cancer, the deep model parameters were estimated using data from the HIP project for breast cancer screening [van Oortmarssen 1990a] and the assumptions where checked against the Dutch screening projects in Nijmegen and Utrecht [van Oortmarssen 1990b]. The cost-effectiveness and quality of life results were calculated for several breast cancer screening strategies [van der Maas 1989, de Koning 1991]. The MISCAN model for breast cancer screening has also been employed to predict the impact of breast cancer screening on clinical medicine [de Koning 1990], and the impact on quality-adjusted life-years [de Haes 1991]. Furthermore, the observed mortality reduction in five Swedish breast cancer-screening trials were analyzed [de Koning 1995]. Recently, the Dutch breast cancer program was evaluated [Fracheboud 1998] and population trends were surveilled [van den Akker-van Marle 1999]. For both breast cancer and cervical cancer, MISCAN analyses have been used extensively for policy decision concerning the respective screening programs.

The MISCAN-COLON model was developed in 1996 in a project for the National Cancer Institute in the United States. It was shown that the model is useful for the systematic evaluation of evidence from studies as well as for prospective evaluation of effects and costs of screening [Loeve 1998]. A basic model quantification for the evaluation of colorectal cancer screening was constructed, the “expert MISCAN-COLON model”. The assumptions in this model have been based on literature and expert opinion. A sensitivity analysis was performed during the project in which the cost-effectiveness of a number of screening strategies was explored under several sets of assumptions. The considered screening tests were rehydrated FOBT, unrehydrated FOBT, sigmoidoscopy, colonoscopy, and barium enema. The main conclusion from the sensitivity analysis was that, based on 1998 knowledge, none of the screening tests could be shown to be preferable to any other for all plausible assumptions. Furthermore, the Minnesota Colon Cancer Control Study, the Kaiser sigmoidoscopy program and the National Polyp Study were simulated using the MISCAN-COLON model. This demonstrated that the program is flexible and detailed enough to specify the design, population and attendance patterns in each of the studies. Although the expert MISCAN-COLON model gives a good fit of part of the results of the studies, large discrepancies were discovered. The results of the comparison of the expert MISCAN-COLON results with the observations in the National Polyp study data are described in Chapter 5. Results of the comparison of the expert MISCAN-COLON model with the Minnesota Colon Cancer Control Study and the Kaiser sigmoidoscopy program are reported in Chapter 8. This thesis mainly describes the research performed after this project.

Outline of the thesis

In this thesis, aspects of colorectal cancer screening and of surveillance (follow-up) of adenoma patients are studied.

Models have been developed to estimate the effects and cost-effectiveness of fecal occult blood screening strategies that were not studied in population-based studies. All models assume that every cancer in the population has an equal chance to bleed at a particular moment. This assumption has been questioned, because part of the preclinical cancers may never bleed, thus giving rise to systematic false-negative test results. This is especially important if the colorectal cancer mortality reduction by annual FOBT screening is estimated from results of biennial FOBT screening, such as the results from the Funen and Nottingham trial. Therefore, a research question addressed in this thesis is: *What is the impact of systematic negative results on the colorectal cancer mortality reduction achieved by FOBT screening?*

Sigmoidoscopy screening seems expensive, because sigmoidoscopy is an expensive test compared with FOBT and diagnostic colonoscopy is needed after positive sigmoidoscopy. However, it is plausible that endoscopic screening reduces colorectal cancer incidence by the removal of adenomas. This will not only reduce colorectal cancer mortality, but also induces savings in colorectal cancer treatment. It is not known to what extent the savings in colorectal cancer treatment compensate the costs of an endoscopic screening program. Therefore, a research question addressed in this thesis is: *Are the costs of sigmoidoscopy screening compensated by induced savings?*

The effectiveness of endoscopic screening depends to a large extent on the natural history of the adenoma-carcinoma sequence. It is not possible to observe the natural history of the adenoma-carcinoma sequence directly, because adenomas and colorectal cancer are treated upon detection. The natural history of the adenoma-carcinoma sequence can indirectly be studied by investigating which assumptions on the adenoma-carcinoma sequence best explain observations in endoscopic screening studies and studies of surveillance in patients who had adenomas removed during endoscopy. An important study in this respect is the National Polyp Study. A research question addressed in this thesis is: *What natural history assumptions best explain the National Polyp Study results?*

A consequence of screening for colorectal cancer is that adenomas will be detected in many individuals. Currently, it is recommended that individuals who have had adenomas removed undergo regular colonoscopic surveillance because they are at high risk for colorectal cancer. The surveillance interval strongly depends on the colorectal cancer risk after adenoma removal. If patients in whom adenomas have been removed have a lower or equal colorectal cancer risk as the general population, the adenoma patients do not require more intensive surveillance than the screening performed in the general population. Therefore, the last research question addressed in this thesis is: *What is the colorectal cancer risk in patients with removed adenomas?*

In Chapter 2, the MISCAN-COLON model is described. The structure of the natural history model and the assumptions in the initial model quantification were decided upon during expert meetings. This model is called the “expert MISCAN-COLON model”.

In Chapter 3, the impact of systematic non-bleeding asymptomatic colorectal cancers on the estimated program sensitivity and mortality reduction from FOBT screening is calculated. In Chapter 4, the costs and savings due to sigmoidoscopic screening are estimated for the United States using the expert MISCAN-COLON model. In Chapter 5, MISCAN-COLON model variants are explored to find assumptions that are consistent with the National Polyp Study observations. This provides insight in the natural history of the adenoma-carcinoma sequence. In Chapter 6, the colorectal cancer risk after polypectomy is investigated by reviewing all studies on colorectal cancer risk after polypectomy. Furthermore, the colorectal cancer incidence in 553 consecutive adenoma patients of the Slotervaart hospital, Amsterdam was studied. Chapter 7 reports colorectal cancer incidence in the years after adenoma removal based on the Palga registry, the nation-wide pathology registry in the Netherlands. This provides estimates of the colorectal cancer risk after adenoma removal with the current Dutch practice. In Chapter 8 of this thesis, the results from the previous chapters are discussed, new developments in colorectal cancer screening are described, and the possibility to screen for colorectal cancer in the Netherlands is discussed.

2

The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening

Abstract

A general model for evaluation of colorectal cancer screening has been implemented in the microsimulation program MISCAN-COLON. A large number of fictitious individual life histories are simulated in each of which several colorectal lesions can emerge. Next, screening for colorectal cancer is simulated, which will change some of the life histories. The demographic characteristics, the epidemiology and natural history of the disease, and the characteristics of screening are defined in the input. All kinds of assumptions on the natural history of colorectal cancer and screening and surveillance strategies can easily be incorporated in the model.

MISCAN-COLON gives detailed output of incidence, prevalence and mortality, and the results and effects of screening. It can be used to test hypotheses about the natural history of colorectal cancer, such as the duration of progressive adenomas, and screening characteristics, such as sensitivity of tests, against empirical data. In decision making about screening, the model can be used for evaluation of screening policies, and for choosing between competing policies by comparing their simulated incremental costs and effectiveness outcomes.

Introduction

Colorectal cancer (CRC) is a major cause of cancer-related death in Western countries. About 5% of the population will develop colorectal cancer before 80 years of age, and half of these persons will die of this disease. The presumed natural history of colorectal cancer and the availability of screening tests make colorectal cancer a serious candidate for screening. Theoretically, screening may reduce mortality in two ways. First, detection of an asymptomatic cancer in an early stage may result in an improvement in prognosis. Second, evidence exists that most colorectal cancers develop from adenomas and that this process takes years. Detection and removal of adenomas may thus lead to prevention of cancer. Potentially useful screening tests for colorectal cancer and its precursors are fecal occult blood tests (FOBT), flexible sigmoidoscopy (FSIG), barium enema (BE), and even colonoscopy (CSCPY) [Winawer 1997]. Randomized controlled trials of fecal occult blood testing have shown that screening can reduce colorectal cancer mortality [Mandel 1993, Hardcastle 1996, Kronborg 1996].

Evidence on the effectiveness of BE and endoscopic-based screening strategies, however, is still limited, and the size of health benefits and costs is uncertain. The incomplete knowledge of the natural history of the disease makes it difficult to estimate the effectiveness of screening strategies. As has been shown for other cancers, mathematical models can be useful to test hypotheses about the incidence and natural history of disease and screening characteristics and subsequently to make predictions of the (cost-) effectiveness of screening strategies [van Oortmarssen 1995a].

Both Eddy [Eddy 1990] and Wagner *et al.* [Wagner 1996] have constructed models to estimate the potential benefits and costs of several CRC screening strategies, including FOBT, FSIG, BE, and CSCPY screening. Eddy describes the model as a set of differential equations and developed computer programs in which the equations are solved by numerical integration, while the model of Wagner *et al.*, initially developed at the U.S. Congressional Office of Technology Assessment, is a discrete-time Markov model. Both models make simplifying assumptions about important aspects of the natural history of CRC. For example, in both models the possibility that a person develops more than one polyp in a lifetime is not included. In reality this is common and it will influence the outcomes of screening policies considerably. The single lesion assumption implies that surveillance after screen detection of a polyp is useless because surveillance is intended to discover further polyps. For correct interpretation of data and to make precise estimates on the effect of screening this aspect should be included in an evaluation model. The only model so far that does include this aspect is the model of Geul *et al.* [Geul 1997] which has been designed for the evaluation of sigmoidoscopy screening. However, it concentrates on the multiplicity of lesions and not on the natural history of colorectal lesions, which makes it, for instance, inappropriate for studying the effect of the earlier detection of invasive cancers.

The model presented in this article allows for less simplification and therefore more flexibility in exploring various assumptions and can be used to simulate all candidate

screening tests. This model is a version adapted to colorectal cancer of the MISCAN (MIcrosimulation SCreening ANalysis) microsimulation model for the evaluation of screening [Habbema 1984], which is being used for breast cancer and cervical cancer screening evaluation [van der Maas 1989, de Koning 1991, van Ballegooijen 1992]. The structure of the model will be explained in the next section. Next, a formal description will be provided. Section “The program” deals with the computer program and the input and output of the program. Next, an example of the use of the model will be given. In the last section special features of the model are emphasized and possible applications of the model are discussed.

Structure of the MISCAN-COLON program

A general model for evaluation of colorectal cancer screening is implemented in the microsimulation program MISCAN-COLON. Two parts of the program can be distinguished, a natural history part and a screening part. In the natural history part of the program, life histories are generated during which colorectal polyps and cancer may develop and sometimes cause death and in which no screening takes place. In the second part of the program, screening for colorectal cancer is simulated. Screening will change some life histories. The aggregated changes in life histories constitute the effectiveness of the screening. The effects of different screening policies can be compared by applying them to identical life histories. If one is solely interested in modeling the natural history of the disease, the screening part is not necessary. The stochastic model underlying the simulation is specified in the input of the program. The input relates to demographic characteristics (e.g., the life table), the epidemiology and the natural history of the disease (e.g., the duration of preclinical cancer), and the characteristics of screening (e.g., the sensitivity of the screening test).

Natural history without screening

The MISCAN-COLON program simulates a population of fictitious individuals in each of which several colorectal lesions can emerge. Lesions may proceed through three phases, as shown in the upper part of Figure 2.1: a preclinical noninvasive polyp phase, a preclinical invasive cancer phase, and a clinical cancer phase. These phases can be further subdivided. More than one lesion can develop in a person and an anatomical site in the bowel is assigned to each lesion. Each lesion can develop into cancer, and it is possible that a person has more than one cancer. The history of a lesion consists of its successive stages and the ages of the individual at which transitions between stages occur. This lesion history is generated for each lesion in a person, and can result in death from colorectal cancer. If none of the lesions is lethal, the person dies from other causes. The life history of a person, consisting of the age and stage at diagnosis and age and cause of death, is based on these lesion histories. Figure 2.2.a gives an example of a person who develops three lesions in his life. The resulting life history is shown at the bottom line.

Life histories are simulated in a number of steps. First, an age at death from other causes is generated from the life table for a person. It is assumed that the age at death from

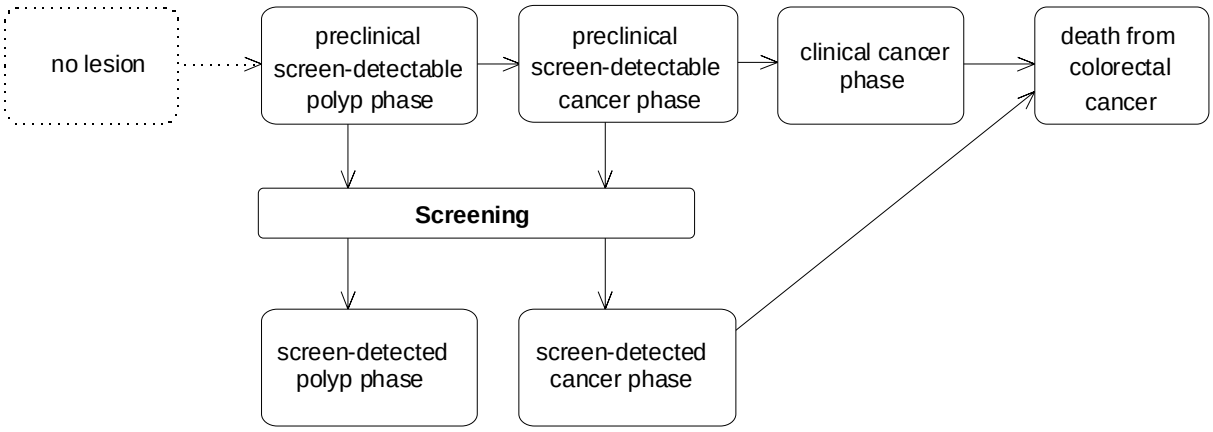

Figure 2.1 The phases through which a colorectal lesion can develop in a situation with screening.

other causes is not affected by colorectal cancer. Subsequently the lesion histories are generated. The moment of onset of a lesion is defined as the moment at which the lesion becomes screen-detectable. In reality, this moment can depend on the screening test used. Usually, the first stage after onset (the initial stage) is a preclinical noninvasive (polyp) stage. Many lesions will still be in the polyp phase when the person dies from other causes, just as lesion 1 in Figure 2.2.a. A lesion can transit from a preclinical polyp stage to a preclinical cancer stage. A preclinical cancer stage is a stage in which the lesion is already invasive, but not yet diagnosed. It is possible that a lesion is invasive from the beginning, such as lesion 2 in Figure 2.2.a, that represents cancer without a preceding polyp. When signs and symptoms lead to diagnosis of a cancer, the lesion enters the corresponding clinical cancer stage and a survival time is generated. The survival of a lesion after diagnosis depends on the stage of the cancer. In Figure 2.2.a lesion 2 is diagnosed at age 60. Lesion 2 has a survival time of 10 years, leading to death from disease at age 70.

The life history of a person begins in a stage without disease (see bottom line of Figure 2.2.a). A person transits to a clinical stage at the first age at which a lesion is diagnosed clinically, i.e., age 60 for the person in Figure 2.2.a, when lesion 2 is diagnosed. It is assumed that during the diagnostic process, following clinical detection, all other cancers in the bowel will be found as well. Therefore, the person enters the clinical stage of the most developed cancer at the time of diagnosis. The age of death of a person with clinical cancer is the age at death from colorectal cancer or the age at death from other causes, whichever comes first. New lesions that appear after clinical diagnosis of cancer, such as lesion 3 in Figure 2.2.a are accounted for in the survival of the clinically diagnosed cancer. In Figure 2.2.a the person dies at age 70 from colorectal cancer. The person would have died at age 80 from other causes and thus loses 10 life-years due to colorectal cancer.

Screening

A screening policy consists of the ages at which screening examinations are scheduled, the period of screening, the screening tests used at each examination, and the diagnostic follow-up scheduled after a positive test. The sensitivity of screening and diagnostic tests may differ for lesions in different disease stages. If a lesion in a preclinical detectable

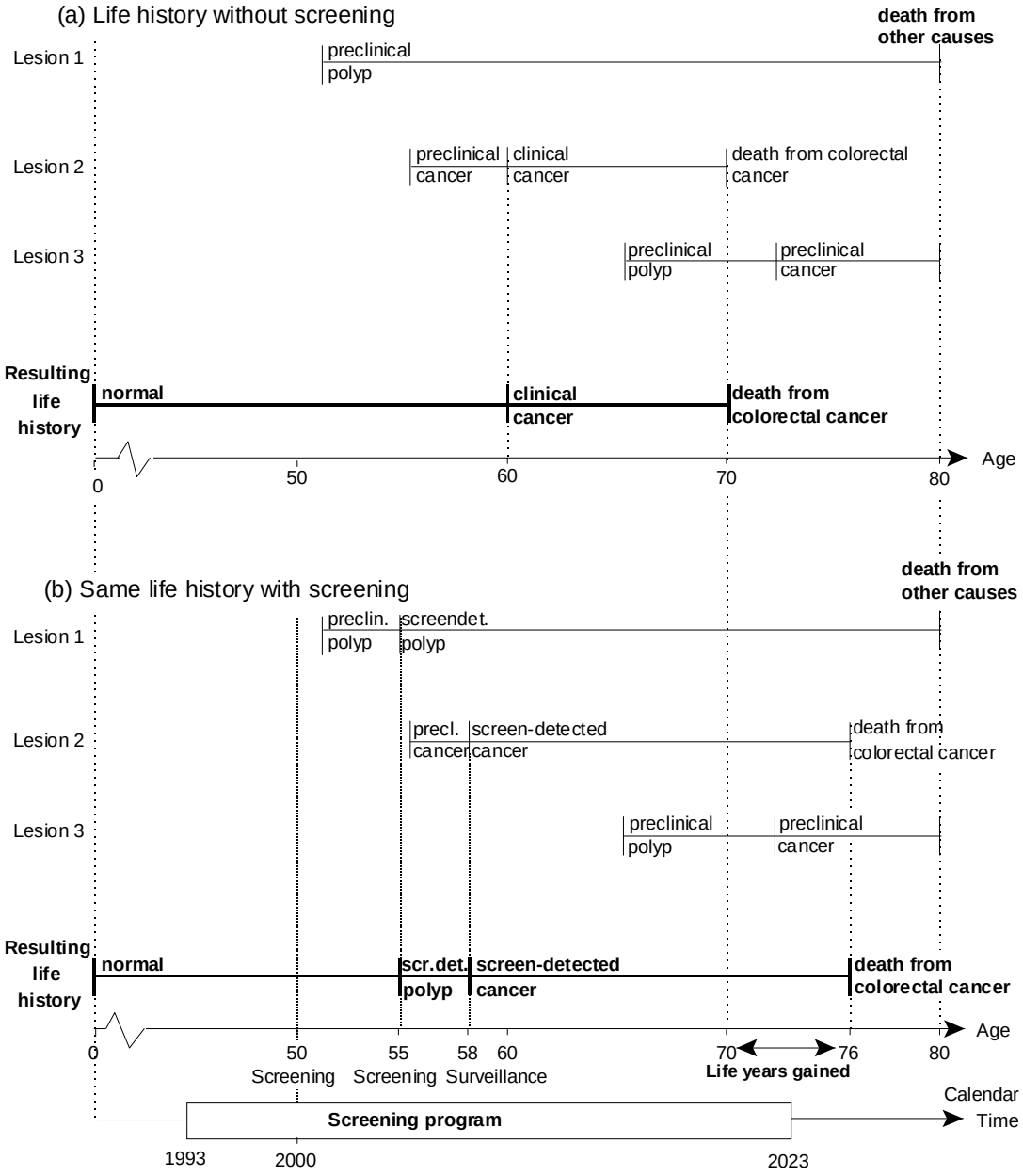

Figure 2.2 (a) An example of a life history for a person who develops three lesions over his life in a situation without screening; **(b)** The life history of (a) in a situation with screening.

stage is missed at a screening, then the result of the screening is false-negative. If a lesion is missed because of a difficult localization (in a fold of the bowel), it is likely that the tumor will be missed again at the next screening. This can be modeled as a systematic negative test result for the lesion.

Figure 2.1 shows that a screen-detected preclinical lesion transits from the preclinical phase to the corresponding screen-detected phase. A person enters the screen-detected stage of the furthest progressed lesion that was found during screening and diagnostic follow-up. This might be a lesion different from the one that was initially detected by the screening test. For instance, detection of a polyp by sigmoidoscopy screening followed by diagnosis of a proximal cancer at subsequent colonoscopy leads to

a transition to screen-detected cancer in the life history. Not all lesions present will necessarily be detected during follow-up tests.

If only noninvasive stages are found, it is assumed that all screen-detected lesions are removed, that their development stops, and that they will not lead to colorectal cancer death. The follow-up after diagnosis of a polyp can be modeled as a surveillance scheme, i.e., a strategy with tests and intervals different from those used in the screening policy. It is assumed that after detection of cancer, further diagnostic and therapeutic management is accounted for in the survival. For each cancer detected at screening, the age at death from disease can be affected in five different ways by screen detection in the model: the death from disease can be prevented, the age at death from disease can be delayed, the age at death from disease can be the same as in the situation without screening, a person can die of the operation after screen detection, or a new survival after screen detection can be generated independent of the age at death from disease without screening.

In Figure 2.2.b the life history of Figure 2.2.a is represented in a situation with screening. At the bottom of the figure a time axis is shown, indicating that screening is performed between 1993 and 2023. At the first screening at age 50 no lesion is found and the test is true-negative. Lesion 1 is detected at the second screening at age 55 as a polyp. The lesion is removed, and the person transits to the corresponding screen-detected polyp stage and is kept under surveillance. At the first surveillance test at age 58 lesion 2 is detected in a cancer stage, and a new age at death from disease is generated for lesion 2. In this example, colorectal cancer death is delayed from 70 to 76 years of age. Again, it is assumed that lesions that appear after diagnosis of a cancer, such as lesion 3 in Figure 2.2.b, are accounted for in the survival of the detected cancer. Screening tests and surveillance tests after detection of cancer are therefore not simulated explicitly.

The resulting life history is represented at the bottom line. After the second screening the person is in a screen-detected polyp stage. At surveillance detection of lesion 2 the person transits to a screen-detected cancer stage. The person dies from the disease due to lesion 2 at the age of 76 and still loses 4 life-years because of death from colon cancer. Screening resulted in a gain of 6 life-years in this person.

Formal description of the model

In this section a formal description of the model is presented. The most important parameters of the model are summarized in Tables 2.1 and 2.2. Many parameters are optional. This means that, depending on the available knowledge and data and on the purpose of the simulation, the model can, within certain limits, be made as simple or complex as needed.

Table 2.1 Summary of demography and natural history parameters in MISCAN-COLON and the assumptions used in the example. Two screening policies are simulated in the example: FSIG, 3-yearly sigmoidoscopy screening; FOBT, biennial unrehydrated FOBT screening.

Parameter	Model specification in example
Population size	1,000,000 in 1993
Strata in the model	1
Life tables of death from other causes than colorectal cancer	Based on age-specific mortality rates in U.S. population in 1989-1991
Distribution of births over calendar years	Based on the age distribution in SEER data in 1993 and mortality rates in U.S. population in 1989-1991. No births after 1993
Types of lesions	1 type, with initial stage adenoma ≤5mm
Stages in a lesion	See Figure 2.3
Parameters of the distribution of the risk index	Average risk, 1; variance, 2
Age-specific preclinical incidence rates	Based on clinical incidence stage distribution in SEER data in 1978 and a prevalence of adenomas in 15% of the population in age group 50-59 to 33% in age group 70+
Site distribution	Site distribution of clinical cancers in SEER data in 1978
Transitions from each stage	Based on clinical stage distribution in SEER data in 1978 and size distribution of adenomas in autopsy studies (40% ≤5mm, 40% 6-9mm, 20% ≥ 10mm), assumed to be independent of site
Durations in stages	*Dwelling time distributions in preclinical stages:* exponential *Mean total duration of preclinical stage of lesions that grow into cancer:* 20 years *Mean duration of preclinical cancer stage:* 3.6 years *Survival in clinical stages:* Based on SEER data
Correlation between durations	100% between durations in preclinical stages

Table 2.2 Summary of screening parameters in MISCAN-COLON and the assumptions used in the example. Two screening policies are simulated in the example: FSIG, 3-yearly sigmoidoscopy screening; FOBT, biennial unrehydrated FOBT screening. Surv. CSCPY=Surveillance colonoscopy.

Parameter	Model specification in example			
Screening policy in each stratum	First and last year of screening: 1993-2023 FSIG: Screening ages (50, 53, 56,.., 74) and FSIG test FOBT: Screening ages (50, 52,.., 80) and unrehydrated FOBT test			
Specificity and sensitivity of each screening or surveillance test		FSIG (%)	FOBT (%)	Surv. CSCPY (%)
	Specificity	100	98	100
	Sensitivity for adenoma ≤5mm	75	2	80
	Sensitivity for adenoma 6-9mm	85	2	85
	Sensitivity for adenoma ≥10mm	95	5	95
	Sensitivity for cancer	95	60	95
Dependency between tests	No dependency			
Site-dependent sensitivity	No site dependency			
Reach of each screening test	*FSIG:* 100% of the tests reach the end of the rectum; 75% of the tests reach the end of the transversum (including flexures); 0% reaches farther than 25% of the transversum (including flexures) *FOBT:* Sensitive for lesions in whole colon			
Sensitivity of the diagnostic test	100% in all preclinical stages			
Diagnostic follow-up after a positive result for each test and each preclinical stage	Yes			
Prognosis after screening	*After screen-detection of a polyp:* 100% cure *After screen-detection of a cancer:* new survival based on stage-specific survival of clinical cancer			
Follow-up after screen-detection of each noninvasive stage	*After a positive screening test or surveillance test without lesions detected or only adenomas ≤ 5mm detected:* Number of years without screening (surveillance interval): 5 Next test after surveillance interval: screening test *After a positive screening or surveillance test with adenomas 6-9mm and/or ≥ 10mm detected:* Number of years without screening (surveillance interval): 5 Next test after surveillance interval: surveillance CSCPY			
Attendance to screening in each stratum	100%			

Demography

The model simulates an age-structured population, which enables public health evaluation of health benefits and costs of screening during a certain calendar period. Simulating a birth cohort is also possible.

Every person in the simulation has a date of birth and an age of death from other causes. The dates of birth and of death from other causes are generated from a distribution of births over calendar years and from a life table. The population may be divided into several groups (strata), where each stratum can have its own distribution of births and its own life table. Strata can be used to model differences in cancer risk and other characteristics in the population (see the next section). The relative size of each stratum must be specified.

Epidemiology and natural history

Development of lesions. Lesions may proceed through three phases: a preclinical noninvasive polyp phase, a preclinical invasive cancer phase, and a clinical cancer phase, as shown in the upper part of Figure 2.1. In the situation with screening, screen-detected phases are added. These phases can further be subdivided, to take account of differences in prognosis, differences in detectability, and differences in follow-up policy. The stages are ranked in order to determine the most "advanced lesion" found at screening or at clinical diagnosis.

Preclinical incidence. It is possible to define up to three different types of lesions. For example, adenomas and hyperplastic polyps can be distinguished. Each type is defined in the model by a unique initial stage. It is not necessary that subsequent stages are unique as well. For example, lesions of type 1 could start as a small adenoma and then develop into cancer, while lesions of type 2 start immediately as cancer. It is assumed that lesions of different types develop independently in a person. New lesions may start to develop until the age of death from other causes is reached.

The assumption that colorectal lesions are randomly distributed among the human population, with all individuals having the same hazard of obtaining new lesions, would result in a Poisson distribution for the number of lesions in persons of a certain age. However, variation in genetic and environmental factors will result in heterogeneity in preclinical incidence. These risk differences between individuals in a population are modeled by introduction of a risk index for each individual. A high risk index indicates a relatively high probability to develop lesions. For each person a risk value is determined by a random drawing from a gamma distribution, which is a continuous probability distribution ranging between 0 and infinity [Law 1982]. The mean and variance of this gamma distribution can be specified for every stratum and each type of lesion. A high-risk group can be modeled by a stratum with a high mean of the risk index. The risk to develop lesions of a type is proportional to the risk index for that type and the age-specific preclinical incidence rate for that type (see Appendix 2.A).

The gamma distribution for risk in the population results in a negative binomial distribution of colorectal lesions at a given age in the population [Mood 1974]. This distribution is widely used in the conceptually similar field of modeling parasite burden in

the population [de Vlas 1993]. If the variance of the gamma distribution for risk indices is small, the distribution of colorectal lesions at a certain age will approach a Poisson distribution.

Anatomical site. In the model, each lesion in a person is located at a specific anatomical site. For each type of lesion the distribution of lesions over the anatomical parts of the large bowel can be specified. The anatomical site of a new lesion is assumed to be independent of the anatomical site of previous lesions. The anatomical site of a lesion is indicated by the part of the bowel in which the lesion is situated, e.g., the sigmoid, and a percentage that indicates the localization within this part. Transitions, durations, and the sensitivity of screening tests can but need not depend on anatomical site. Furthermore, the distribution of depth of insertion of a screening test can be specified. The ability to take anatomical site into consideration is important for the evaluation of sigmoidoscopy and colonoscopy screening, where a screening test is characterized by a depth of insertion. For example, a person can have a lesion in the sigmoid at a distance of 60% (of the length of the sigmoid) from the end of the sigmoid. If a sigmoidoscopic examination does not reach the entire sigmoid, but only the last 30% of the sigmoid, this lesion will not be found. In addition, this aspect is important for the evaluation of FOBT screening because there are indications that the sensitivity of FOBT depends on the site [Macrae 1982].

Transitions and durations of lesions. After the onset of a lesion in an initial stage, the history of a lesion is simulated by successively generating a subsequent stage and a duration in the present stage. For each stage probabilities to transit to subsequent stages are specified. Transition probabilities can depend on age of the person and anatomical site of a lesion. Each possible transition between two stages has its corresponding probability distribution of the dwelling time in the present stage. Four types of dwelling time distribution functions are currently implemented in the model: a constant duration (parameter: mean), an exponential distribution (parameter: mean), a Weibull distribution (parameters: shape, mean), and a piecewise uniform distribution (parameters: (a_i, b_i), $i = 1, .., n$, where a_i is a dwelling time and $b_i = P(\text{dwelling time} \leq a_i)$). The mean of exponentially or Weibull distributed dwelling times can depend on age and anatomical site. Simple model specifications will assume independence between the dwelling time in a stage and a dwelling time in a previous stage. However, it is possible to specify that durations in successive stages are correlated. This correlation is characterized by a parameter with values between -1 and 1. Independence of dwelling times is indicated by a value of 0; deterministic dependency on the previous dwelling time is indicated by ± 1.

Screening

Screening policy and attendance. In the model, mass screening is offered at predefined ages in a specific calendar period. Individuals without clinical colorectal cancer are invited and a proportion, defined by attendance probabilities, will accept the invitation and attend screening. Screening policies can differ between strata and are defined by the calendar period of mass screening, the ages at which persons are invited to screening, and the screening tests at each age. Up to three screening tests can be used. Attendance probabilities of screening may differ between strata and are specified for each screening

age. Attendance probabilities should be given separately for persons who came to the previous screening and for persons who did not.

Characteristics of screening tests. A screening test has a positive or negative result. The probabilities on each outcome depend on the absence or presence of lesions. For each screening test the specificity is defined, i.e., the probability of a negative result in persons without lesions. In persons with lesions, test results are generated for each lesion independently. For each screening test and each preclinical stage the probability of a positive test result due to a lesion in that stage (sensitivity) is specified. A screening result is positive if one or more lesions are detected.

It is possible to specify that the sensitivity of the screening test depends on the anatomical site of a lesion. It is assumed that the site dependency of a test does not differ between preclinical stages. The site dependency relation of a test is specified by a sensitivity multiplication factor for each site. The site-specific sensitivity is obtained by multiplying the sensitivity value of the screening test by the multiplication factor. In addition, it is possible that a screening test reaches only part of the bowel. In that case, the probability to reach sites in the bowel can be specified. For each application of a screening test in a person, the depth of insertion is generated. Only lesions within reach can be found during the screening test.

After a positive screening test, a diagnostic test can be performed. In practice, a diagnostic test is not always performed after a positive screening test. For example, in sigmoidoscopy screening, a finding of a small tubular adenoma does not always lead to diagnostic colonoscopy. Therefore, the stages that lead to a diagnostic test can be specified. Furthermore, it is possible to define the sensitivity of the diagnostic test for each stage separately and to make it site-dependent.

A screening examination may consist of more than one screening test. In case of complete independency between test results, the probability of a positive test result is independent of the results of the same test in previous screenings, and independent of the results of other tests applied in the same or in previous screening rounds. The assumption of independent test results is only realistic in case false test results occur randomly, e.g., in case of unnoticed and temporary technical or human error. Part of the errors will occur more systematically. The possibility of systematic errors has been implemented in the MISCAN-COLON program via the concept of systematic test results (see Appendix 2.B). In this concept, the result of a test has two components: one random and one systematic. The errors in the random component occur by chance, i.e., the outcome of the test is independent of all other test results. Errors in the systematic component of test results are correlated. Both systematic negative and systematic positive test results may occur. Systematic test results can occur per:

- person. For example, it is possible that an FOBT is always positive in a person.
- test examination. For example, it is possible that all small polyps within reach are missed at sigmoidoscopy because of bad bowel preparation.
- lesion. For example, a lesion can be missed systematically because of a difficult localization in the bowel.

Screening tests can be specified to share systematic results. For example, rehydrated and unrehydrated FOBT tests may differ in sensitivity level but could have the same systematic results.

Prognosis after screening. In this section screening is defined as the combination of the screening examination and, if applicable, further diagnostics after a positive test result. After a positive screening result all screen-detected polyps are assumed to be removed and cannot lead to further development of the disease. Thus, any cancers that would have eventually developed from these screen-detected polyps are totally cured. The possible prognostic consequences after a positive test result for a cancer are:

- Total cure. The person will not die of the screen-detected cancer.
- Delay in moment of death. The moment of death from disease due to the screen-detected cancer is postponed. The period of delay is drawn from a dwelling time distribution.
- No change in moment of death. It can be specified that although a new (screen-detected) stage is entered at the moment of the positive test result, the moment of death from disease of the lesion does not change.
- Operation mortality. A probability of immediate death after a positive screening can be defined.
- New survival after screen detection, independent of the moment of death in the situation without screening. With this option one can use observed stage-specific survival distributions after screen detection. The prognosis after screen detection of cancer is specified by the probabilities of each consequence. These can differ between cancer stages. If several synchronous cancers are detected at screening, an independent prognostic consequence is generated for each cancer.

Follow-up after screening. Several follow-up strategies are possible in persons who had a positive screening examination, but in whom no cancer was found:

- The person returns to the screening program and is invited to the next screening round as usual. This can, for example, be applied to persons in whom only small adenomas were found.
- The person will not be screened for several years. After this period the person returns to the screening program and is invited for screening at the next screening age. This can be useful to model the screening of persons with a false-positive FOBT test. These persons underwent colonoscopy and no lesions were found, leading to a low risk for cancer in the following years.
- The person will be kept under surveillance. The surveillance interval, i.e., the period between two surveillance tests, can be specified. Surveillance continues until no lesions are found. Subsequently, the person is invited for screening at the next screening age. In this way it is possible to simulate monitoring of persons with large or villous adenomas who are considered to be at high risk for colorectal cancer.

The program

The total MISCAN-COLON package consists of two programs: (1) the actual simulation program, and (2) a post-processing program for processing simulation output. A user interface for preparation of input is available. All programs are written in Delphi (Borland) and require Windows '95. Simulation of 100,000 individuals that are screened six times takes about 60s on a 133-MHz Pentium. The average time needed depends on the complexity of the disease process and the number of screenings performed in the population.

The random number generator, based on [l'Ecuyer 1991], is divided into two disjoint random number subsequences and requires two initial seeds. For each source of randomness the number of the random number subsequence can be specified, which can be used to reduce variance between simulation runs. For each new person in a simulation, the starting points of the random number generators are calculated. In this way, as long as the same initial seeds are used in simulations, in every simulation the same random number sequence is assigned to a life history. This reduces the variance between simulation runs. The output of the actual simulation program consists of two files, a file for postprocessing and a standard output file. The postprocessing file contains all

Table 2.3 Contents of file with MISCAN-COLON output for postprocessing.

For each risk group[a] by year
Number of first and repeat invitations and screenings, and the number of surveillance tests
Number of prevented and detected cancers by screening and surveillance and number of prevented deaths from colorectal cancer*
Number of life-years gained by the screening program*
Number of positive and negative results of screening and surveillance examinations in each preclinical stage (by age group)
Number of entries to each stage (by age group)
Number of life-years and number of life-years lost by the disease (by age group)
Number of disease-specific deaths and the number of nonspecific deaths (by age group)
Totals over the whole simulated time period, for the situation with and without screening discounted by three percentages, for example 0, 3, and 5%
Number of first and repeat invitations, number of screening examinations, and number of surveillance tests
Number of positive and negative diagnostic follow-up tests after a positive screening test
Number of entries and life-years in clinical and screen-detected stages
Number of disease-specific deaths
Number of life-years lived
Number of life-years lost by disease

* optional

[a] A risk group is a clustering of strata

important outcomes for the evaluation of a screening policy (see Table 2.3). It contains results per year, useful for detailed analysis, and aggregated totals over time that can be used directly by the postprocessing program. The output in this file can be subdivided into maximally three groups of strata. The preclinical stage assigned to a positive screening or surveillance test is defined by the most advanced stage found by the test or during its diagnostic follow-up. The preclinical stage assigned to a negative test is the most developed stage within reach of the screening test. The age groups into which the output is divided, the reference year for discounting, and the discount percentages can be specified. For any clinical stage, the annual number of entries and the number life-years can be tabulated in the output file on demand. The standard output file contains a summary of the input specifications and additional output data if desired, such as incidence and prevalence per age group. Extra output can easily be added to both output files.

The post-processing program uses the discounted totals over time in the post-processing output file to calculate the costs and effects of a screening policy. Costs are assigned to screening tests, diagnostic tests, surveillance tests, and cancer treatment. For example, treatment costs are divided into costs for initial therapy in the first 6 months, costs of palliative care in the last 6 months, and yearly costs of continuous care of colorectal cancer patients. The postprocessing program calculates costs per life-year gained and costs per prevented death using three discount percentages.

Example

As an illustration, the MISCAN-COLON model is used to simulate two screening strategies in the American population from 1993 until 2023. One strategy is 3-yearly FSIG

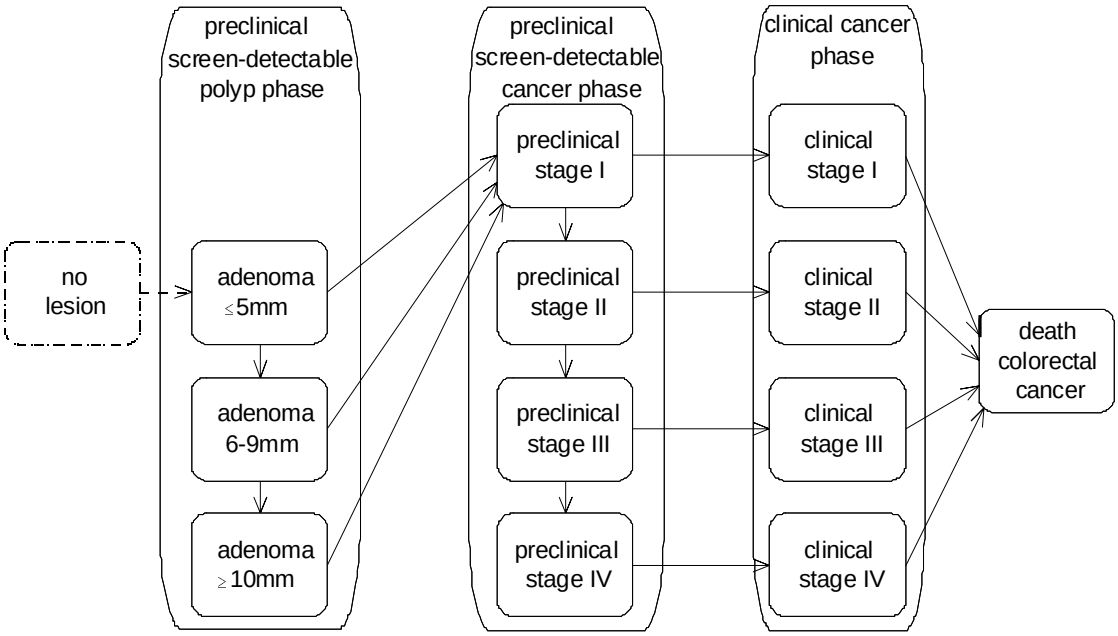

Figure 2.3 The subdivision of the phases in Figure 2.1 as used in example. The polyp phase is subdivided into size categories. The preclinical and clinical cancer phases are subdivided into AJCC stages.

Table 2.4 Predicted undiscounted totals in example per 1,000,000 persons in the 1993 U.S. population, assuming 100% attendance. The screening was performed in 1993 to 2023.

	3-yearly FSIG	Biennial unreh. FOBT	No screening
First invitations	645,800	674,100	0
Repeat invitations	2,345,600	4,183,200	0
Screening examinations	2,921,800	4,829,600	0
Surveillance tests	69,600	27,700	0
Positive diagnostic follow-up tests after screening	148,400	40,300	0
Negative diagnostic follow-up tests after screening	127,800	76,700	0
Entries in clinical stages I-IV	50,500	54,500	62,700
Entries in screen-detected stages I-IV	1,100	5,300	0
Life-years in clinical stage I-IV	404,100	443,600	506,200
Life-years in screen-detected stages I-IV	15,700	66,000	0
Colorectal cancer deaths	22,600	25,200	27,900
Total number of life-years	43,729,400	43,689,900	43,655,600
Life-years lost by disease	303,600	343,100	377,500

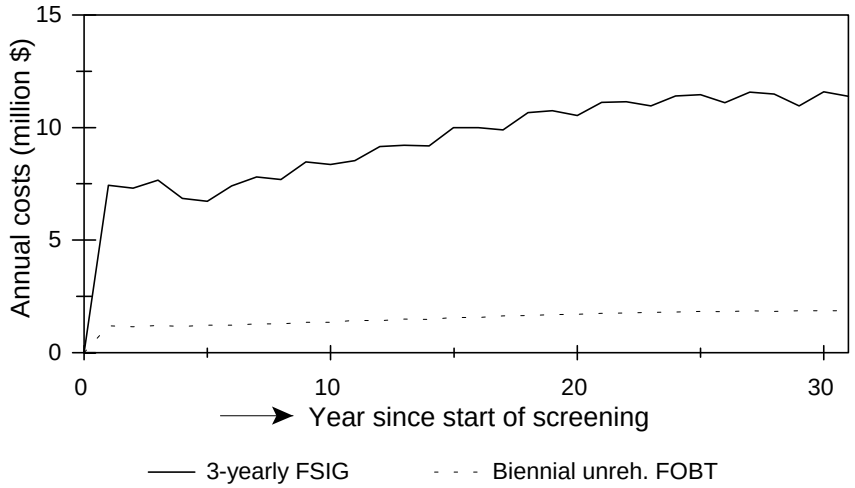

Figure 2.4 Predicted annual costs of screening tests of sigmoidoscopy screening and unrehydrated FOBT screening in example per 1,000,000 persons in the 1993 U.S. population, assuming 100% attendance. The screening was performed in 1993 to 2023.

screening between ages 50 and 74; the other strategy is biennial unrehydrated FOBT screening between ages 50 and 80. Preliminary, but in our opinion not implausible, assumptions about the natural history and screening characteristics were implemented. Parameter values are based on literature and expert opinion. Model assumptions were established in two working meetings of experts at the National Cancer Institute (Bethesda, MD). Some aspects, such as the clinical incidence in the situation without screening and survival after clinical detection, are based on Surveillance, Epidemiology and End Results (SEER) data of the National Cancer Institute in the United States. A summary of the assumptions is given in Tables 2.1 and 2.2. In Figure 2.3 the assumed natural history of

colorectal cancer is presented. The adenoma stages are subdivided according to size, while the cancer stages are based on the AJCC classification.

In Table 2.4, the simulated totals per 1,000,000 persons in the 1993 U.S. population over the whole simulated time period in this example are shown for 3-yearly sigmoidoscopy screening, biennial unrehydrated FOBT screening, and no screening. Figure 2.4 displays the annual costs of the screening program for both strategies. Only the costs of the screening tests are taken into account. The costs of the FSIG program are much higher than the costs of the FOBT program. Figure 2.5 shows the annual mortality reduction due to the screening program. The fluctuations in mortality reduction are due to the stochastic character of the simulation. As an indication, the estimated mortality reduction is based on a simulation with a mean number of 295 colorectal cancer deaths per year. The mortality reduction by the FSIG program is higher than the mortality reduction by the FOBT program. In the first few years of screening the mortality reduction is less than 0 in both programs. This is due to the fact that in the model some people die during their lead time (e.g., by an operation). After these years considerable mortality reduction occurs, and the reduction achieved by FSIG screening is higher than that by FOBT screening under the assumptions. After the end of both screening programs the mortality reduction decreases gradually.

The assumptions in the model can be changed to assess the sensitivity of the model. For instance, when the dwelling time distribution between preclinical incidence of an adenoma and the clinical diagnosis of the subsequent cancer is assumed to be constant instead of exponentially distributed in this model, the simulated number of colorectal cancer deaths prevented by the screening strategies is doubled.

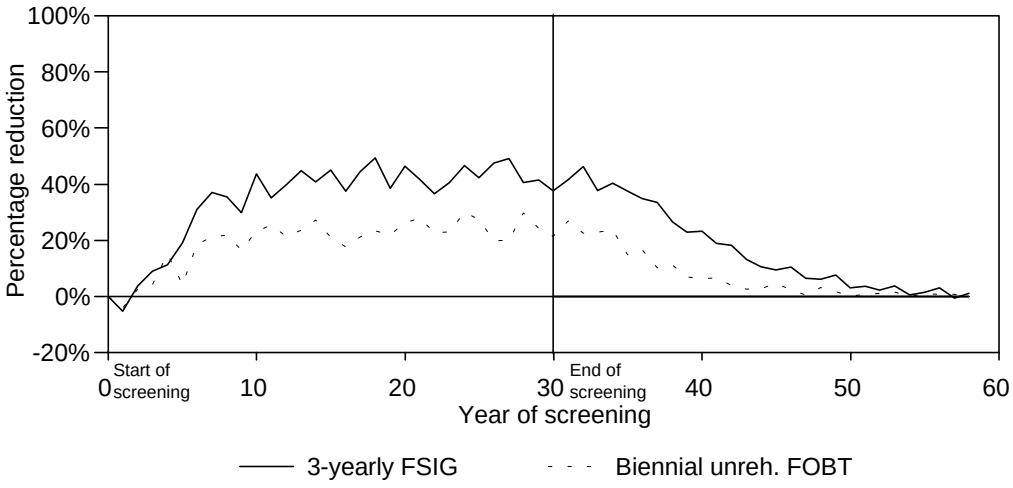

Figure 2.5 Predicted annual percentage colorectal cancer mortality reduction by sigmoidoscopy screening and unrehydrated FOBT screening in example in the 1993 U.S. population, assuming 100% attendance. The screening was performed in 1993 to 2023.

Discussion

The three main purposes of a screening model are analysis of data, testing of hypotheses, and evaluation of screening policies. Use of the MISCAN-COLON model for colorectal cancer screening will be similar to use of MISCAN models for breast and cervical cancer screening.

First, the model will be used to analyze data from screening studies. Reliable use of a model in prospective evaluation of complex screening policies will be possible when the model is sufficiently validated. For instance, the breast cancer model was used for a model-based analysis of the HIP project for breast cancer screening [van Oortmarssen 1990a], and was checked against the Dutch screening projects in Nijmegen and Utrecht [van Oortmarssen 1990b]. In addition, the mortality reductions in five Swedish breast cancer-screening trials were analyzed [de Koning 1995]. For cervical cancer screening similar analyses were carried out [Habbema 1985, van Oortmarssen 1992, van Oortmarssen 1995b].

For colorectal cancer, the program is being employed to evaluate and possibly improve upon preliminary assumptions by analyzing available data. The MISCAN-COLON program is being used to simulate the Colon Cancer Control Study of FOBT screening in Minnesota and the sigmoidoscopy screening performed by the Kaiser Permanente in northern California. Comparison of simulated and observed results will indicate which combinations of parameter values are, and which ones are not, in agreement with the observed results. Next, data from the National Polyp Study [Winawer 1993b] will be analyzed. Analysis of these datasets will help to narrow down the uncertainty about model parameters describing the natural history of polyps and colorectal cancer and the characteristics of screening tests. Furthermore, it will indicate the level of complexity required in the model. For instance, analysis of the Minnesota Colon Cancer Control Study will address the question of whether systematic test results of FOBT screening should be incorporated in the model.

Furthermore, the model can serve to test different hypotheses about the natural history of polyps and colon cancer and about the impact of screening. For example, in a cervical cancer screening model three hypotheses about regression of preinvasive cervical cancer were tested against data from the British Columbia cohort study [van Oortmarssen 1991]. An adequate fit was achieved by assuming that regression of preinvasive lesions is age-dependent.

Finally, a validated model can be used for evaluation of screening strategies. The MISCAN model for breast cancer screening has been employed to predict the impact of breast cancer screening on clinical medicine [de Koning 1990] and the impact of breast cancer screening on quality-adjusted life-years [de Haes 1991]. In addition, cost-effectiveness and quality of life results were calculated for several screening strategies [van der Maas 1989, de Koning 1991]. The MISCAN model for cervical cancer screening has been used to estimate cost-effectiveness of cervical cancer screening in The Netherlands [Koopmanschap 1990a, Koopmanschap 1990b, van Ballegooijen 1992] and to explore the potential value of HPV testing for cervical cancer screening [van

Ballegooijen 1997]. In the MISCAN-COLON model all kinds of assumptions on the natural history of colorectal cancer and screening and surveillance strategies can easily be incorporated. Therefore, the MISCAN-COLON model can serve to make predictions for the cost-effectiveness outcomes of screening policies, as shown in the example. Furthermore, the model is well suited for performing sensitivity analysis on the outcomes. For example, the effect of possible site dependency of the sensitivity of FOBT [Macrae 1982] on the predicted cost-effectiveness can be calculated. After the model has been validated by analysis of data, it will be used for the evaluation of effectiveness and cost-effectiveness of screening policies and of surveillance policies after polyp removal.

Acknowledgment

Work was supported by Research Contract NO1-CN-55186 with the National Cancer Institute in Bethesda, Maryland. The authors thank Martin Brown, Project Officer of the National Cancer Institute, the participants of the working meeting June 5-7, 1996, in Bethesda, and Sake de Vlas, Department of Public Health, Erasmus University Rotterdam, for their contributions.

Appendix A. Preclinical incidence of lesions

For each individual life history and each type of lesion *i* a risk index R_i is drawn from a gamma distribution denoting the risk to develop lesions of type *i*. The gamma distribution is based on two parameters α and β, with mean=$\alpha \cdot \beta$ and variance=$\alpha \cdot \beta^2$. The density function of the gamma distribution is:

$$f(x) = \begin{cases} \dfrac{\beta^{-\alpha} x^{\alpha-1} e^{-x/\beta}}{\Gamma(\alpha)} & \text{if } x > 0 \\ 0 & \text{otherwise} \end{cases}$$

Let a_0 denote age 0 or the age at which the last lesion of type *i* developed. The onset rate $h_i(a)$ is the probability to develop lesions of type *i* at age *a* in a person in which the risk index equals 1. The onset rates are assumed to be "piecewise constant", i.e., constant over age intervals denoted by (b_u, b_{u+1}), u = 1, 2, ... The corresponding accumulated preclinical incidence between age a_0 and *a* in a person with risk index R_i equals:

$$H_i(a, a_0) = R_i \int_{a_0}^{a} h_i(y)dy$$

The probability distribution for the age a_i at which a new lesion of type *i* develops is:

$$\Pr(a_i \le a) = 1 - \exp\left[-H_i(a, a_0)\right]$$

The age at which a new lesion of type *i* develops is calculated by solving this equation, where the probability is replaced by random number *u*, uniformly distributed between 0 and 1.

Appendix B. Systematic test results

Before simulation of screening in a person, random numbers u_s are generated that will be used to determine whether results of a screening test are systematic. Systematic test results can occur per person. Therefore, a random number u_{st} is drawn for each test *t*. Systematic test results can also occur per lesion. Therefore, a random number u_{stl} is drawn for each test *t* and each lesion *l*. The random numbers u_s for systematic test results per examination are generated when examination is simulated. If two tests *v* and *w* have the same systematic results, the random number for the systematic results are equal: $u_{sv} = u_{sw}$ and $u_{svl} = u_{swl}$ for each lesion *l*.

At each screening and surveillance examination in a person, the test results for each test are generated as follows.

If the person does not carry lesions at the time of the examination: For each test *t* a tuple (P_{st}, N_{st}, P_t) is given for persons without lesions, denoting the probability of a systematic positive result, the probability of a systematic negative result, and the probability of a nonsystematic positive result if the result is not systematic. If $u_{st} \leq P_{st}$, the random number for systematic test results in this person is lower than the probability of a systematic test result in a person, the test is systematically positive. If $u_{st} \geq 1 - N_{st}$, the generated random number for systematic test results in this person is higher than 1 – the probability of a systematic test result in a person, the result is systematically negative. If the result is not systematic, a random number *u* is generated. If $u \leq P_t$, the result of the test is positive, else the result of the test is negative.

If the person does carry one or more lesions at this age: For each test *t* and each preclinical stage *E* a tuple (P_{spEt}, N_{spEt}, P_{seEt}, N_{seEt}, P_{sEt}, N_{sEt}, P_{Et}) is given, where P_{spEt} is the probability of a systematic positive test result in a person in which the most developed lesion within reach of the test is in stage *E;* N_{spEt} is the probability of a systematic negative result of test *t* in a person in which the most developed lesion within reach of the test is in stage *E*; P_{seEt} is the probability of a systematic positive result of test *t* at a screening examination where the most developed lesion within reach is in stage *E;* N_{seEt} is the probability of a systematic negative result of test *t* at a screening examination where the most developed lesion within reach is in stage *E;*P_{sEt} is the probability of a systematic positive result of test *t* for a lesion in stage *E*; N_{sEt} is the probability of a systematic negative result of test *t* for a lesion in stage *E*; and P_{Et} is the probability of a positive result of test *t* due to a lesion in stage *E* if no systematic result.

The results are generated separately for each screening or surveillance test *t*. At each screening in a person, the stage E_{max} of the most developed lesion within reach of test *t* is determined. First, it is decided whether the test has a systematic result for this person. Consequently, it is determined whether the test has a systematic result due to the examination moment. Finally, if this does not lead to systematic results, for each lesion separately it is determined whether the test has a systematic result. If the test has no systematic result for the lesion, the random result is generated.

If $u_{st} \leq P_{spEt}$, where $E = E_{max}$, the result of test *t* is systematic positive for the person.

If $u_{st} \geq 1 - N_{spEt}$, where $E = E_{max}$, the result of test t is systematic negative for the person.

If no systematic result of test t for the person, a random number u_t is generated to decide whether the test result is systematic at this test moment.

If $u_t \leq P_{seEt}$, where $E = E_{max}$, then the result of test t is systematic positive.

If $u_t \geq 1 - N_{seEt}$, where $E = E_{max}$, then the result of test t is systematic negative.

If still no systematic result for test t, then the test results are evaluated for each lesion l separately. E denotes the stage of lesion l.

If $u_{stl} \leq P_{sEt}$, then the result of test t is systematic positive for lesion l.

If $u_{stl} \geq 1 - N_{sEt}$, then the result of test t is systematic negative for lesion l.

If there is no systematic result of the test, a random number u for lesion l is generated. If $u \leq P_{Et}$, then the test result for lesion l is positive, otherwise the test result for lesion l is negative.

3

Impact of systematic false-negative test results on the performance of fecal occult blood screening

Abstract

The impact of systematic false-negative test results on mortality reduction and on program sensitivity of annual fecal occult blood testing in ages 50-84 years is explored using a microsimulation model. We made calculations for test sensitivities of 80, 50 and 30%. In order to reproduce a cancer detection rate of 2.2 per 1000 at the first screening, the corresponding mean preclinical sojourn times had to be 1.42, 2.30 and 3.84 years, respectively. The fraction systematic results among the false-negative results is varied between 0 and 100%. With 80% test sensitivity, the reduction in mortality due to screening decreases from 25% without systematic results to 23% when all false-negative results are systematic and the program sensitivity decreases from 63 to 58%. With 30% test sensitivity, mortality reduction decreases from 21 to 11% and program sensitivity decreases from 52 to 27%. The impact of systematic false-negative test results is important if annual FOBT screening is considered.

Introduction

The effect of fecal occult blood test (FOBT) screening on colorectal cancer mortality partly depends on the sensitivity of the test. A major factor in the effect of FOBT screening is the early detection of preclinical cancer, although polyp removal after a positive fecal occult blood test may occasionally prevent cancer incidence and death. A proportion of the prevalent cancers at a fecal occult blood test will be missed because they do not bleed. Lesions not detected at one application of the test may be detected at a subsequent screening. However, the total fraction of preclinical cancers detected by a fecal occult blood screening program is limited by the short duration of the early preclinical stages of cancer and by the fraction of the preclinical cancers that never bleed and thus will never be detected by fecal occult blood tests.

The favorable effect of fecal occult blood screening on colorectal cancer mortality has been shown in several randomized controlled trials [Mandel 1993, Hardcastle 1996, Kronborg 1996, Mandel 1999]. However, trials are expensive and only a limited number of screening strategies can be evaluated in a trial. Therefore, models have been developed to estimate the effects and cost-effectiveness of other fecal occult blood screening strategies [Eddy 1990, Wagner 1996, Winawer 1997, Gyrd-Hansen 1998, Whynes 1998]. These models can be used to study alternative screening strategies that have not been evaluated in randomized trials, such as annual unrehydrated FOBT screening, or screening with new immunochemical tests [Castiglione 1996]. All these models assume that every cancer in the population has an equal chance to bleed at a particular moment. This assumption has been questioned [Lang 1997, Ransohoff 1997], because some preclinical cancers may never bleed, thus giving rise to systematic false-negative test results. It was stated that this phenomenon could have an important impact on results, and that it should be subjected to sensitivity analysis in order to make recommendations and should be subject to validation in future studies [Ransohoff 1997]. We will explore the impact of systematic false-negative test results using the MISCAN microsimulation model for evaluation of screening [Loeve 1999] which has been used to estimate the costs and savings of sigmoidoscopy screening [Loeve 2000].

Methods

Systematic test results are defined here as persistently false-negative results of FOBT in individuals with preclinical colorectal cancer due to the failure of the cancer to bleed. The impact of systematic negative results on mortality reduction and program sensitivity of annual FOBT screening is studied with the MISCAN microsimulation model. This model includes an option that test results depend on previous test outcomes [Loeve 1999].

The sensitivity of most fecal occult blood tests for adenomas is low [Abdul Fattah 1997, Nakama 1997a] because they rarely bleed. Thus, adenomas are mainly detected by chance at endoscopy following a coincidentally positive FOBT [Ransohoff 1990, Ahlquist 1993] and the issue of never-bleeding adenomas is not important. Therefore, we will

neglect the possibility of detecting adenomas and we only need to make assumptions about the test sensitivity for cancer, about the sojourn time of preclinical cancer and about the potential occurrence of systematic negative test results.

The test sensitivity for cancer is assumed to be constant throughout the preclinical cancer phase, as in other models [Eddy 1990, Wagner 1996, Winawer 1997]. Test sensitivity refers to the sensitivity at the first screening. Because widely divergent estimates have been reported, simulations are done for three levels of test sensitivity of a hypothetical fecal occult blood test for cancer: 30, 50 and 80%. The upperbound of 80% is chosen because test sensitivity estimates based on the first screening in two randomized controlled trials were of this size [Mandel 1993, Kewenter 1994]. Estimates around the lowerbound of 30% have also been reported [Ahlquist 1993, Allison 1996]. Test sensitivity of both the Hemoccult test and the HemoQuant test was estimated to be 26% in patients with prior colorectal cancer [Ahlquist 1993]. Test sensitivity has been estimated to be 37% for Hemoccult II assuming colorectal cancer cases within 2 years after a negative screening to be false-negatives [Allison 1996].

The sojourn time of preclinical cancer is chosen such that the simulated cancer detection rate in the first screening round is 2.2 per 1000 screenings. This 2.2 per 1000 resembles the detection rates found in the trials in Göteborg [Kewenter 1994] and Nottingham [Hardcastle 1996], while other studies found slightly lower or higher rates [Church 1990, Kronborg 1996, Launoy 1997, Towler 1998]. This leads to a mean preclinical cancer duration of 1.42 years in the model variant with 80% test sensitivity, 2.30 years in the model variant with 50% test sensitivity and 3.84 years in the model variant with 30% test sensitivity. The duration of preclinical cancer follows an exponential probability distribution.

The impact on expected mortality reduction and program sensitivity is evaluated for five levels of the proportion of cancers for which negative results are systematic: 0, 25, 50, 75 and 100%. If 0% of the negative results are systematic, then each preclinical cancer bleeds at random and the probability that a cancer bleeds at a test moment is equal to the test sensitivity. If 100% of the negative results are systematic then a proportion of the preclinical cancers, equal to the test sensitivity, always bleed and will be detected by fecal occult blood tests, while the remaining cancers never bleed and thus will never be detected by the screening test. For instance, in the variant with 80% test sensitivity for cancer and 25% of the negative results being systematic, it is assumed that $0.25 \times (1 - 0.8) = 0.05$ of all preclinical cancers will always be missed because they never bleed. The other cancers have at each screening a probability of $0.8 / (1 - 0.05) = 0.84$ of being detected.

It is assumed that the age-specific incidence of colorectal cancer without screening equals the US Surveillance, Epidemiology and End Results (SEER) incidence in 1978, when almost no screening was performed [Ries 1997]. The long-term disease-specific survival after clinical detection of cancer is assumed to be 50% on average, similar to the survival in 1974-1979 in the SEER registry [Ries 1997]. We do not distinguish disease stages and, for predicting the mortality reduction, we assume that of those who would die of the disease without screening, 50% will be cured by early detection. This figure is based on the Minnesota study, where the 13-year survival is approximately 60% in the

control group and approximately 80% in the screen-detected cases in the annually screened group [Mandel 1993], indicating that approximately 50% of the cases that would die from colorectal cancer without screening will survive when they are screen-detected. This figure could be biased by the lead-time in the screen-detected cases. However, the 10-year and 13-year survival in the screen-detected cases do not differ, suggesting that nearly all mortality from colorectal cancer will occur within 10 years after diagnosis.

Results are based on a simulation of 1,000,000 persons with an age distribution as for the 1993 US population. In this population, annual fecal occult blood screening is performed at ages 50 to 84 years in the period 1993-2022. Compliance with screening and diagnostic follow-up is assumed to be 100%. The mortality reduction in the total US population and the program sensitivity during the screening program are calculated for all variants. The mortality reduction in the total population is calculated as the proportion among all deaths from colorectal cancer during the screening period 1993-2022 that is prevented by the early detection of cancer. The numerator of the program sensitivity consists of all screen-detected cancers. The denominator of the program sensitivity consists of all preclinical cancers in the screened age group that are prevalent at some moment during the screening period.

In a sensitivity analysis, two major model assumptions are varied: the duration distribution of preclinical cancer and the detection rate at first screening. In a model variant, the preclinical cancer duration is not exponentially distributed, but distributed according to a Weibull distribution with shape parameter 2, similar to shapes used in the modeling of cervical cancer [van Oortmarssen 1991], which results in less variance in preclinical cancer duration than an exponential distribution. In some FOBT studies, a detection rate around 1.8 instead of 2.2 per 1000 was observed in the first screening round [Kronborg 1996, Launoy 1997]. Therefore, in another model variant, detection rate in the first screening round is assumed to be 1.8 per 1000. In both model variants, simulations are performed for test sensitivity levels of 30 and 80%. In the model variants with a Weibull distributed preclinical duration, the mean duration is the same as the mean preclinical duration in the model described above. For the model variants with a detection rate at first screening of 1.8 per 1000, the mean preclinical cancer duration is shortened to approximately 1.8/2.2 = 82% of the duration in the baseline model and is 3.2 years when the test sensitivity is 30% and 1.17 years when the test sensitivity is 80%.

Results

Figure 3.1 and Figure 3.2 show the mortality reduction and program sensitivity of annual fecal occult blood screening for different levels of the fraction systematic test results among false-negatives in model variants with 30, 50 and 80% sensitivity. One would expect that the mortality reduction is half the program sensitivity, as each screendetected cancer has a probability of 50% to be cured. However, the mortality reduction is less, because it is calculated over all colorectal cancer deaths between the ages 0 and 100 years, while the program sensitivity is calculated in the screened age group of 50-84 years.

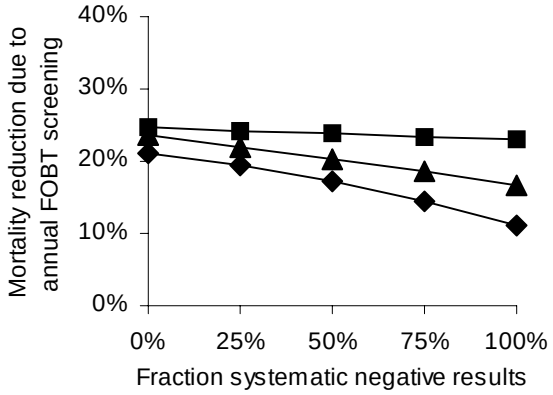

Figure 3.1 Predicted impact of the fraction systematic negative test results on the mortality reduction of annual fecal occult blood (FOBT) screening during the period 1993-2022 in the population aged 50-84 years. ■, 80% test sensitivity and a mean preclinical sojourn time of 1.42 years; ▲, 50% test sensitivity and a mean preclinical sojourn time of 2.30 years; ◆, 30% test sensitivity and a mean preclinical sojourn time of 3.84 years.

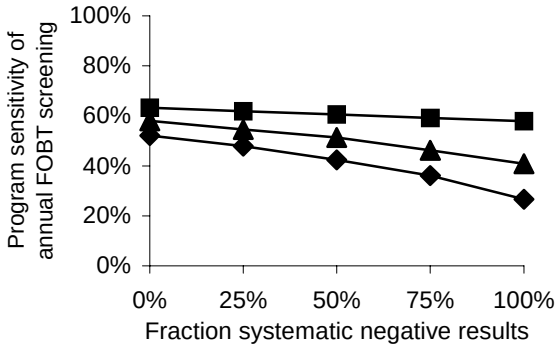

Figure 3.2 Predicted impact of the fraction systematic negative test results on the program sensitivity of annual fecal occult blood (FOBT) screening during the period 1993-2022 in the population aged 50-84 years. ■,80% test sensitivity and a mean preclinical sojourn time of 1.42 years; ▲, 50% test sensitivity and a mean preclinical sojourn time of 2.30 years; ◆, 30% test sensitivity and a mean preclinical sojourn time of 3.84 years.

Furthermore, some of the prevented colorectal cancer deaths will occur after the end of the screening program.

As can be seen from Figure 3.1 and Figure 3.2, the impact of systematic false-negative results is limited if the test sensitivity of a fecal occult blood test is high (80%). The program sensitivity decreases from 63% to 58% while the mortality reduction decreases from 25% to 23%. This modest impact can be explained by the short mean duration of preclinical cancer, resulting in a low number of screenings at which a cancer can be missed. Moreover, even if all negative results are systematic, only 20% of all cancers do not bleed. In the case of a low test sensitivity (30%), the impact of systematic false-negative test results is larger and it can reduce the screening performance by approximately 50% both with respect to mortality (from 21 to 11%) and program

sensitivity (from 52% to 27%). In the variant with 50% test sensitivity, systematic results can reduce mortality by 29% from 24 to 17%.

The variant with 80% test sensitivity gives a higher mortality reduction compared with a 30% test sensitivity, although the detection rate at the first screening round is equal. This is caused by the large number of interval cancers in the variant with 30% test sensitivity, in spite of a longer duration. In the variant with 80% test sensitivity and no systematic results, the program sensitivity is only 63%. One would expect the program sensitivity to be higher than the test sensitivity, because some of the lesions will be present at more than one screening examination. Nevertheless, this effect is contrabalanced by lesions that will develop and be clinically diagnosed in the interval between two screenings. In the case of 80% test sensitivity, the mean duration of preclinical cancer has to be very short in order to satisfy the detection rate at the first screening round, and 28% of the cancers will arise and be clinically diagnosed in the interval between two screenings. Therefore, the program sensitivity is lower than the test sensitivity. In the variant with 30% test sensitivity and no systematic results, the program sensitivity is 52%. Here, the program sensitivity is higher than the test sensitivity because of a longer mean duration of preclinical cancer.

The effect of systematic negative results in the model variants of the sensitivity analysis is similar to the effect in the baseline model. In the model with a Weibull distributed duration with shape 2 and 30% test sensitivity, systematic results can reduce mortality reduction by 52% from 27 to 13%. In these models, the number of fast-growing cancers is smaller than in the baseline model. Therefore the probability that a missed preclinical cancer is detected at a next screening is higher than in the baseline model which causes the high mortality reduction compared with the baseline model. In the models with a detection rate of 1.8/1000 and 30% test sensitivity, systematic results can reduce mortality by 45% from 20 to 11%. Here, the mean preclinical duration is shorter than in the baseline model and therefore the probability that a missed preclinical cancer is

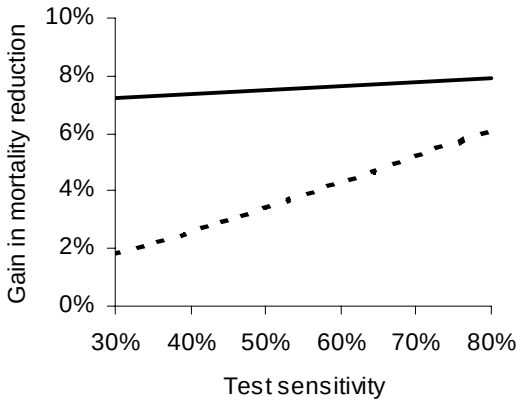

Figure 3.3 Predicted absolute gain in reduction of colorectal cancer mortality by changing the interval of fecal occult blood screening from 2 years to 1 year. ———, 0% systematic negative results; • • • •, 100% systematic negative results.

still preclinical at a next screening is smaller. Therefore, the impact of systematic negative results is slightly smaller when the detection rate is smaller than in the baseline model.

When the mortality reduction of biennial FOBT screening is known from observations, what is the extra gain in mortality reduction if the number of screens is doubled by shortening the screening interval from 2 years to 1 year? Figure 3.3 shows that the extra mortality reduction would be approximately 8% if no systematic negative results occur, but less when all negative results are systematic. For example, if the test sensitivity is approximately 62%, as estimated by Gyrd-Hansen *et al.* [Gyrd-Hansen 1997], annual screening instead of biennial screening reduces colorectal cancer mortality by 8% and by 4–5% when all false-negative results are systematic.

Discussion

Ransohoff *et al.* [Ransohoff 1997] stated that "it is clear that how many cancers bleed and how often they bleed at detectable levels are critical features affecting the success of fecal occult blood tests and newer tests". This study shows that systematic false-negative FOBT results may have considerable impact on the expected mortality reduction and program sensitivity of annual FOBT screening, in particular when the test sensitivity is low.

In this paper, a simplified model has been used to estimate the effect of systematic false-negative test results on mortality and program sensitivity. For example, 100% participation in screening and diagnostic follow-up is assumed, while in reality performance is sub-optimal because some people come only occasionally to screening or do not comply with diagnostic follow-up. Another simplification is that the impact of polyp removal and systematic negative results of polyps is neglected. This has been discussed in the Methods section. Furthermore, it is assumed that the sensitivity is constant during the entire preclinical period. The potential impact of systematic negative test results is smaller in a situation where the test sensitivity shows a considerable increase during the preclinical period than in a situation with a constant test sensitivity and the same mean test sensitivity and preclinical duration. In the first situation, the probability is higher that a missed cancer will be detected at repeat screening because the probability that a screening test is positive increases during the preclinical period.

To estimate the fraction systematic negative results from observed data, one could examine the interval cancer rate in the years after first and repeat screening in combination with the background incidence. If the fraction of systematic negative results is 100%, only new cancers will be detected at repeat screening and the cancers missed at previous screenings will surface in the first years after the repeat screenings, resulting in relatively high interval cancer rates after repeat screening. For example, in the model variant with 30% test sensitivity, the incidence rate after the fourth screening varies between 50 and 75% of the background incidence rate, depending on the percentage systematic test results. Two FOBT trials published data on cancer incidence after each repeat screening [Gyrd-Hansen 1997, Moss 1999]. However, the impact of systematic negative results would have been small in these studies, even if all negative results were systematic, because biennial screening was performed and thus most preclinical cancers at repeat screenings were new.

Furthermore, in both studies the number of interval cancers after repeat screening is too small to reliably estimate the proportion of systematic negative results.

If the fraction systematic results is estimated from observations, the estimated fraction systematic results depends on the assumed distribution of preclinical cancer duration. Preclinical cancers that will never be detected by fecal occult blood tests because of systematic negative results can equivalently be modeled as cancers with a preclinical duration of 0. Consequently, when it is assumed that many fast-growing preclinical cancers occur, the estimated fraction of systematic negative results is smaller than estimated assuming no fast-growing preclinical cancers. In our study, the duration of preclinical cancer is assumed to be exponentially distributed, similar to other colorectal cancer screening models [Gyrd-Hansen 1997, Launoy 1997].

A crude estimate for the percentage of systematic negative FOBT results can be derived from the results of FOBT in samples on 3 consecutive days. One study of immunochemical FOBT calculated the test sensitivity of the one-, two-, and three-sample FOBT in 184 colorectal cancer patients [Nakama 1997b]. FOBT revealed 125 positive results on the first day. If every cancer has the same chance to bleed at a certain moment, 6 patients (3%) would be expected to have three negative test samples. However, as much as 17 patients did not have any positive test samples, and the data are best reproduced when it is assumed that 24% of the negative results are systematic, i.e., 8% of all cancers never bleed. On the one hand, more than half of the patients in that study had symptoms, such as blood loss, and therefore the percentage of systematic negative results in preclinical cancer patients is likely to be higher. On the other hand, the test interval was only 1 day and some of the cancers that systematically did not bleed may bleed if the test is repeated after a few months. This suggests that the percentage of systematic negative results might be lower.

The possibility of systematic negative test results should be considered when recommendations for FOBT screening are derived. Gyrd-Hansen *et al.* [Gyrd-Hansen 1997] estimated the test sensitivity at 62%, and the mean sojourn time at 2.1 years. They suggest that the overall effectiveness of a Hemoccult II screening can be improved significantly by screening more frequently than every 2 years. However, our study shows that the mortality reduction of annual screening might be much lower than expected because of systematic negative results. The impact of systematic negative results is small when the test sensitivity is high. The impact of systematic false-negative tests is important if annual FOBT screening is considered.

Acknowledgement

This work was supported by research contract NO1-55186 with the National Cancer Institute. The authors would like to thank Martin Brown, Project Officer of the National Cancer Institute for his contribution.

4

Endoscopic colorectal cancer screening: a cost-saving analysis

Abstract

Background

Comprehensive analyses have shown that screening for cancer usually induces net costs. In this study, the possible costs and savings of endoscopic colorectal cancer screening are explored in order to investigate whether the induced savings may compensate for the costs of screening.

Methods

A simulation model for evaluation of colorectal cancer screening, MISCAN-COLON, is used to predict costs and savings for the U.S. population, assuming that screening is performed during a period of 30 years. Plausible baseline parameter values of epidemiology, natural history, screening test characteristics, and unit costs are based on available data and expert opinion. Important parameters are varied to extreme but plausible values.

Results

Given the expert opinion-based assumptions, a program based on every 5-year sigmoidoscopy screenings could result in a net savings of direct health care costs due to prevention of cancer treatment costs that compensate for the costs of screening, diagnostic follow-up, and surveillance. This result persists when costs and health effects are discounted at 3%. The “break-even” point, the time required before savings exceed costs, is 35 years for a screening program that terminates after 30 years and 44 years for a screening program that continues on indefinitely. However, net savings increase or turn into net costs when alternative assumptions about natural history of colorectal cancer, costs of screening, surveillance, and diagnostics are considered.

Conclusions

Given the present, limited knowledge of the disease process of colorectal cancer, test characteristics, and costs, it may well be that the induced savings by endoscopic colorectal cancer screening completely compensate for the costs.

Introduction

In the past, it has often been asserted that preventive medical services, including screening, are cost saving. The use of preventive services has sometimes been promoted to reduce health care costs. However, this claim has generally not been supported by detailed analysis. For instance, most well-conducted cost-effectiveness analyses of breast and cervical cancer screening find that the costs of screening tests, of diagnostic follow-up, and of treatment are much larger than the savings in treatment costs [de Koning 1991, Brown 1993, van Ballegooijen 1993].

Colorectal cancer is an important health problem in industrialized countries and comprises 11% of all cancer incidence and 13% of all cancer mortality in the United States [Ries 1998]. Several modalities have been proposed to screen for this disease, including fecal occult blood test, flexible sigmoidoscopy, double-contrast barium enema, and colonoscopy [Markowitz 1997, Winawer 1997]. Three fecal occult blood test trials using Hemoccult tests have shown a reduction in colorectal cancer mortality [Mandel 1993, Hardcastle 1996, Kronborg 1996, Mandel 1999]. Economic evaluations linked to two of these trials have concluded that screening by fecal occult blood test is likely to be cost-effective but not cost saving [Gyrd-Hansen 1998, Whynes 1998]. Cost-effective means that the incremental cost of obtaining a unit of health effect from screening compared with no screening is below an accepted benchmark, while cost-saving interventions result in a net economic savings as well as a savings in quality-adjusted lifeyears [Gold 1996]. The efficacy [i.e., the extent to which medical interventions achieve health improvement under ideal circumstances [Gold 1996]] of endoscopic or barium enema screening has not yet been demonstrated by randomized controlled trials, although several case-control studies suggest that endoscopic screening is associated with a substantial reduction in mortality from colorectal cancer [Selby 1992, Selby 1995, Muller 1995a, Hoff 1996b, Rex 1997a]. One reason that screening by endoscopy has been proposed as a supplement or alternative to fecal occult blood test screening is that the preventive effect of the former is likely to be larger. Invasive cancer and its associated high treatment costs may be prevented through detecting and removing noninvasive adenomas that are generally believed to be precursors of colorectal cancer. The results of ongoing endoscopic trials are expected to become available in several years and will provide more definitive information on the magnitude of this preventive effect [Berry 1997, Brevinge 1997, Atkin 1998]. In this study, we estimate the costs and savings of endoscopic screening by use of a simulation approach.

Methods

The results are based on simulation outcomes of a detailed model for evaluation of colorectal cancer screening (MISCAN-COLON) that has been developed by the Department of Public Health at the Erasmus University Rotterdam, The Netherlands, in cooperation with the National Cancer Institute (NCI) in the United States [Loeve 1999].

The model is an adapted version of a microsimulation model previously used for the evaluation of breast and cervical cancer screening [Habbema 1984, Koopmanschap 1990a, de Koning 1991, de Koning 1995, van Ballegooijen 1997]. At two expert meetings at the NCI 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 (see "Participants" section for the participants of the expert meetings). The validity of this "expert" model is based on observational data, such as clinical incidence and mortality from colorectal cancer [National Cancer Institute 1997] and the size distribution of adenomas in autopsy studies [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993]. The validity of this model has not been tested on a large longitudinal dataset because that is currently unavailable. A sensitivity analysis has been carried out for important uncertain parameters. If no published data are available for an estimate of a parameter, the estimate has been decided upon by the expert panel during the two working meetings that were followed by an e-mail discussion. Using the MISCAN-COLON model [Loeve 1999], it is possible to track costs and induced savings in a hypothetical screening

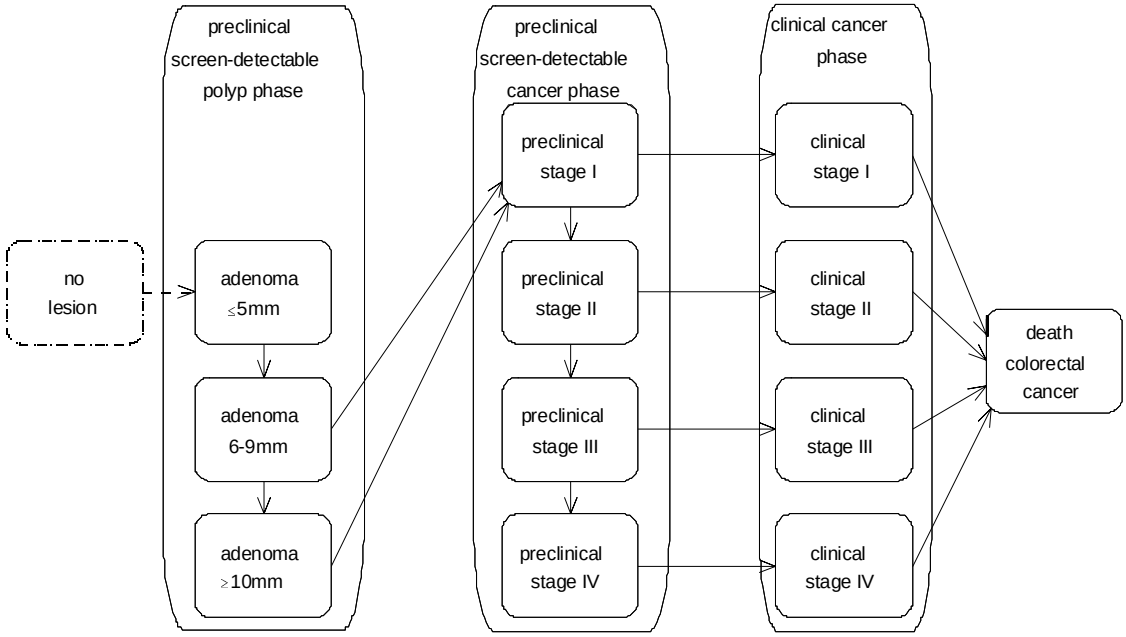

Figure 4.1 Adenoma and cancer stages in the MISCAN-COLON micro-simulation model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for colorectal cancer. Adenomas are categorized by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age. In the expert model, it is assumed that the proportion of progressive adenomas increase from 16% at age 65 years, to 37% at age 75 years, and 96% at age 100 years. In the expert model, it is assumed that 50% of nonprogressive adenomas will remain 6-9mm stage until death and 50% will progress to the ≥10mm stage. For progressive adenomas, it is assumed that 30% will develop through the sequence: ≤5mm adenoma → 6-9mm adenoma → preclinical stage I cancer and that 70% will develop through the sequence ≤5mm adenoma → 6-9mm adenoma → ≥10mm adenoma → preclinical stage I cancer. The mean duration time for progressive adenomas is assumed to be 16.4 years (with an exponential distribution). The mean duration time for cancer is assumed to be 2 years (stage I), 1 year (stage II), 1.5 years (stage III), and 0.8 year (stage IV).

program over an extended period of time. In the following section, the structure of the expert model, the initial model parameter values, and the assumptions in the alternative variants are presented.

Expert model

Structure of the model. In the microsimulation model, persons are simulated in whom one or more colorectal neoplastic lesions may develop. Each lesion is simulated separately, enabling each lesion to have its own natural history. Every lesion is located at a specific site in the colorectal tract, thus enabling simulation of the reach of endoscopic tests.

The disease stages that are distinguished in the adenoma-carcinoma-sequence are shown in Figure 4.1. The adenomas are categorized into size categories: less than or equal to 5mm, 6-9mm, and greater than or equal to 10mm. Most of the adenomas will never grow into cancer in a lifetime. Progressive adenomas will grow into preclinical cancer and will eventually be clinically diagnosed, but a person may die of other causes before that age of clinical diagnosis. The preclinical and clinical invasive cancer stages are subdivided into American Joint Committee on Cancer / International Union Against Cancer stages I-IV [Beahrs 1988]. Clinical stage refers to the stage of cancer that is assigned on clinical detection. Preclinical stage refers to the stage that would be assigned on screen detection for a screen-detectable cancer, whether or not screening actually takes place.

Model of the situation in the absence of screening. It is 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. The average duration of cancer in preclinical stages I-IV is 2 years, 1 year, 1.5 years, and 0.8 year, respectively, which results in a total average duration of 3.6 years because not every cancer reaches stage IV before clinical diagnosis. These sojourn times are 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 [Hardcastle 1996, Kronborg 1996]. All durations are governed by an exponential probability distribution. Durations in each of the invasive cancer stages as well as durations in the stages of the noninvasive adenomas are assumed to be 100% associated with each other, but the durations in invasive stages as a whole are independent of durations in noninvasive adenoma stages that may precede cancer. These assumptions result in an exponential distribution of the total duration of progressive noninvasive adenomas and of the total duration of preclinical cancer, which has also been used in other cancer screening models [Gyrd-Hansen 1997, Launoy 1997]. It is assumed that 30% of the cancers arise from adenomas of 6-9mm and that 70% arise from larger adenomas.

The preclinical incidence of progressive adenomas has been chosen to reproduce the colorectal cancer incidence by age, stage, and localization in the United States in 1978 [National Cancer Institute 1997]. During this period, almost no screening was performed. The size distribution of adenomas over all ages is assumed to be 56% for stages less than or equal to 5mm, 24% for stages 6-9mm, and 20% for stages greater than or equal to 10mm [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993]. The

preclinical incidence of nonprogressive adenomas that will never grow into cancer has varied until the simulated prevalence of all adenomas was about 15% in age group 50-59 years, 27% in age group 60-69 years, and 33% in age group 70 or more years, in agreement with data from the Kaiser study in Northern California [Palitz 1997] and with data from autopsy and colonoscopy studies [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993]. A good agreement with these data is achieved when 86% of the adenomas that arise before age 65 years are nonprogressive and the percentage of nonprogressive adenomas arising after age 65 years decreases gradually to 63% at age 75 years and to 4% at age 100 years. Each individual is assumed to have one level of risk to develop both progressive and nonprogressive adenomas. This risk index follows a gamma distribution where the variance is twice the mean, which results in an adenoma frequency distribution found in autopsies [Williams 1982b].

The anatomic site distribution of both progressive and nonprogressive adenomas and thus of preclinical and clinical cancer is assumed to be equal to the site distribution of colorectal cancers in the United States in 1978 [National Cancer Institute 1997]. The mortality from other causes is assumed to be constant across the simulated years and equal to the mortality in the United States in 1989-1991. The stage-specific survival after the clinical diagnosis of colorectal cancer is taken from the Surveillance, Epidemiology, and End Results registry data for 1975-1993 (see Note) [National Cancer Institute 1997].

Characteristics of screening, surveillance, and diagnostic tests. The reach of screening sigmoidoscopy and surveillance colonoscopy is modeled by use of data from the Kaiser Northern California screening program [Levin 1999]. The sensitivity of surveillance colonoscopy for each lesion within realized reach is assumed to be 80% less than or equal to 5mm, 85% in adenomas 6-9mm, and 95% in adenomas greater than or equal to 10mm and cancers [Hixson 1991, Rex 1997b]. The expert panel decided to assume the same sensitivity for sigmoidoscopy in lesions within reach of the test, except for a slightly lower value of 75% test sensitivity in adenomas less than or equal to 5mm. After a positive test, all lesions will be removed within a short time. The percentage of the population without adenomas or cancer but with hyperplastic polyps, lipomas, or other lesions that lead to polypectomy and pathology after sigmoidoscopy or colonoscopy has been estimated from Kaiser data [Levin 1999]: 5% for sigmoidoscopy and 10% for colonoscopy. These percentages are assumed to be independent of the screening round.

Survival after screen detection. The stage-specific survival of patients with screen-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage [Kronborg 1996]. Removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma. The mortality from, but not the cost associated with, complications after colonoscopy is assumed to be negligible, because data indicate that this mortality is very low [Wagner 1996].

Unit costs. Published estimates of the cost of screening flexible sigmoidoscopy range from $58 [Lewis 1999] to $150 [Lieberman 1995]. The cost of sigmoidoscopy is assumed in this model to be $100. Estimates of colonoscopy without polypectomy range from $150 [Rogge 1994, Gyrd-Hansen 1998] to $1000 [Lieberman 1995], while estimates

of the cost of colonoscopy with polypectomy and pathology range from $150 [Gyrd-Hansen 1998] to $1500 [Lieberman 1995]. The lower estimates reflect unit cost as measured in organized European screening programs or in particular U.S. practices that have placed a premium on achieving efficient delivery of endoscopic procedures. The higher estimates are based on submitted charges in conventional practice settings, a source of data that is generally believed to overstate true costs. In this model, the cost of colonoscopy without polypectomy is assumed to be $300 and cost of colonoscopy with polypectomy and pathology is $400. The rate of nonfatal complications by bowel perforation is assumed to be two per 1000 colonoscopies performed [Lieberman 1996, Neugut 1996], and a perforation induces $30,000 extra costs [Lieberman 1995, Wagner 1996].

The treatment costs of cancer are divided into three categories: 1) the costs for primary cancer treatment in the first six months ($25,000), 2) the costs of continuous care after primary treatment ($2200 per year), and 3) the costs of terminal care before death from colorectal cancer ($16,000 in the last 6 months), on the basis of health maintenance organization data [Fireman 1997]. Treatment costs of adenomas found during screening or surveillance are assumed to consist only of costs for polypectomy and pathology, thus incorporated in costs of diagnostic or surveillance colonoscopy. All costs are expressed, in real terms, in 1993 U.S. dollars; therefore future costs are not inflated. Discounting, to convert future expenditures to present value, is performed at an annual discount rate of 3%, as recommended by the Panel on Cost-Effectiveness in Health and Medicine; i.e., dollars expended *n* years in the future are discounted by a factor of $1/(1.03)^n$ [Gold 1996, Weinstein 1996].

Screening strategy. Calculations are made for sigmoidoscopy screening, delivered at 5-year intervals between the ages of 50 and 75 years, i.e., six screenings. All positive screening tests are followed by a diagnostic colonoscopy. If no lesions or only adenomas less than or equal to 5mm are found, a person will again be screened by sigmoidoscopy after 5 years. Persons in whom adenomas greater than or equal to 6mm are found are invited for surveillance colonoscopy after 5 years, and surveillance is repeated until no lesions are found. Thereafter one is screened according to the normal screening strategy.

Costs and savings. Costs and savings are calculated per person in a simulated dynamic population. The screening program is in operation from 1993 through 2023. Before 1993, individuals are simulated as described previously in paragraph entitled “Model of the situation in the absence of screening”. The simulated 1993 age distribution corresponds to the U.S. 1993 age distribution [National Cancer Institute 1997]. No births take place after 1993. All screening effects are accounted for by continuing the simulation until all individuals have died. The savings of primary treatment, continuous care, and terminal treatment are calculated as the difference in total costs of treatment of clinically diagnosed and screen-detected cancer in the situation without and with screening.

Table 4.1 Assumptions in expert model and assumptions in alternative models.

Assumption	Expert model	Alternative assumption
Dwelling time probability distribution type	Exponential	Constant
Mean dwelling time between onset and clinical diagnosis cancer	20 years	10 years
Percentage cancers preceded by an adenoma	100%	70%
Unit cost of sigmoidoscopy	$100	$50, $200
Unit cost of colonoscopy without polypectomy	$300	$150, $600
Unit cost of colonoscopy with polypectomy	$400	$200, $800

Model variants

The impact of changes in major model assumptions on results is assessed in a sensitivity analysis (Table 4.1). It is not clear whether all cancers are preceded by adenomas or if some lesions grow directly into cancer without a preceding adenoma. Furthermore, the mean and variance of the dwelling time between onset of a progressive adenoma and clinical cancer are uncertain. Therefore, in one model variant, no variation is assumed in duration between the onset of a progressive adenoma and clinical diagnosis of cancer, i.e., a fixed sojourn time of 20 years. In the other model, the average duration between onset of a progressive adenoma and the clinical diagnosis of cancer of 20 years is changed to 10 years, and the percentage of cancers preceded by adenomas is decreased from 100% to 70%. The preclinical incidence of nonprogressive adenomas has been chosen to simulate the same adenoma prevalence and colorectal cancer incidence as in the basic expert model. The costs of screening and surveillance procedures are varied to 50% and 200% of the expert estimate, because of the large range of published cost estimates.

Results

In the first years of the screening program starting in 1993, approximately 50 individuals per 1000 in the U.S. population are screened, and the induced costs of sigmoidoscopy screening are $8500 per year per 1000 individuals in the population. Screening reduces the incidence in 2023 in the age group 50-84 years from 198 to 105 cases per 100,000 person-years, while mortality is reduced from 83 to 37 per 100,000 person-years. In the first years, the induced savings are negligible, and extra treatment costs are induced by early detection of cancer. Later, treatment costs are saved because of prevention of cancers by removal of adenomas during screening. From the 5th year of the program onward, the yearly treatment costs with screening are lower than the treatment costs without screening. When the screening program finishes in year 30, “break-even” occurs by year 35: Cumulative undiscounted costs will be balanced by savings, (Figure 4.2). In the years after cessation of the program, screening costs have stopped, while treatment costs will still be saved. However, in a program of continuing screening, the break-even point will not be reached until the 44th year of the program, as shown in Figure 4.2.

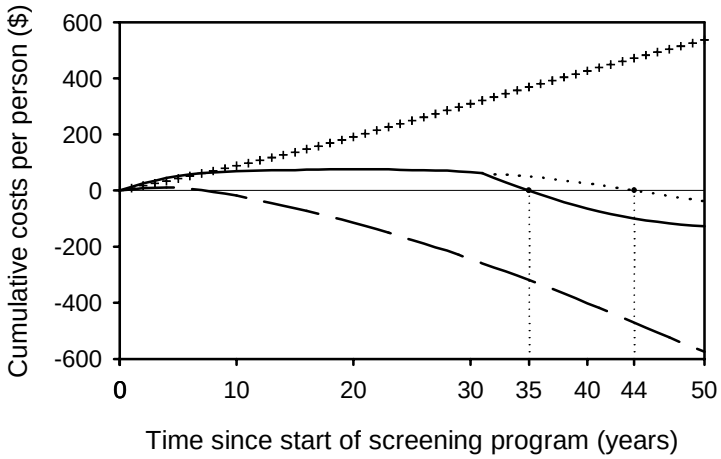

Figure 4.2 Expert model results of every 5-year sigmoidoscopy screening: cumulative undiscounted costs and savings as a function of program years of operation. Break-even (costs = savings) occurs at year 35 for a program that terminates screening at year 30. Break-even occurs at year 44 for a program that continues screening indefinitely. +++++ = cumulative costs of screening, diagnostics, and surveillance of an ongoing program; – – = cumulative difference in treatment costs for screening compared with no screening; ····· = net total costs of an ongoing program; and —— = net total costs of a program that terminates screening after year 30.

Table 4.2 Three percent discounted induced costs and savings ($) of every 5-year sigmoidoscopy screening in age group 50-75 years from 1993 through 2023 per person in the total U.S. population in 1993. Expert model results. *

Costs of screening	129
Costs of colonoscopic diagnostics during screening, including polypectomy and complications	67
Costs of surveillance, including polypectomy and complications	12 +
Total screening induced costs (95% CI)	208 (207-208)
Savings of primary treatment costs	128
Savings of continuous care	39
Savings of terminal treatment	46 +
Total screening induced savings (95% CI)	213 (221-210)
Net screening costs (95% CI)	-5 (-13 to -2)
Life-years gained per 1000 persons	28

* 95% CI= 95% confidence interval (because of stochastic output).

Table 4.2 shows that the 3% discounted costs of a 30-year program of every 5-year sigmoidoscopy screening in the U.S. population are compensated by induced savings in a population setting, resulting in net costs of -$5 per person in the 1993 U.S. population. The costs involved in screening primarily consist of the costs of screening sigmoidoscopies, diagnostic colonoscopy after a positive test, and costs of surveillance after polypectomy. A large amount of costs are saved by the removal of a high-risk non-

invasive adenoma and the prevention of subsequent cancer. For example, for a cohort of 50-year-old persons screened until death, the average undiscounted costs of every 5-year sigmoidoscopy screenings are $743 per person, $508 generated by screening tests, $179 by diagnostic tests, and $56 by surveillance. The average per-person savings in treatment are $1121: $629 saved in primary therapy, $271 in continuous care, and $221 in palliative care. Table 4.2 shows comparable results, averaged across all individuals in the entire U.S. population and discounted at 3% per year. Discounted per person costs average over the entire population are as follows: $129 generated by screening tests, $67 by diagnostic tests, and $12 by surveillance, for a total cost of $208. Savings in treatment are $213: $128 saved in primary therapy, $39 in continuous care, and $46 in palliative care.

Table 4.3 Three percent discounted induced costs and savings of every 5-year sigmoidoscopy screening in age group 50-75 years from 1993 through 2023 per person in the total U.S. population in 1993. Results of alternative models.

Variant	Total costs ($)	Total induced savings ($)	Net costs ($)
Expert model	208	213	–5
Alternative Models			
Constant dwelling time	200	437	–236
10 years dwelling time of progressive lesions and 70% of cancers preceded by adenomas	195	137	+58
Low screening and surveillance costs	103	213	–110
High screening and surveillance costs	386	213	+173

Table 4.3 shows the 3% discounted costs and savings of alternative model variants. Compared with the expert model, the savings of treatment in the variant with a constant sojourn time (20 years) are doubled, resulting in increased cost savings from screening from $5 to $236. This is caused by the absence of fast-growing adenomas that have only a small chance to be detected by screening. In the expert model with exponentially distributed sojourn times, 26% become cancerous within 5 years. In contrast, with a constant sojourn time assumption (an extreme example of a situation with less variability in dwelling times than in the expert model), all progressive lesions are present as noninvasive adenomas for 16 years. In these years, an adenoma can be detected by up to three screening opportunities.

In the variant that assumes a mean value of 10 years for the exponentially distributed sojourn time and assumes that only 70% of the cancers are preceded by an adenoma, the induced savings of treating cancers are lower than in the expert model because sigmoidoscopy has less chance to detect a precancerous lesion before it develops into preclinical cancer. In this variant, 70% of the costs of screening, surveillance, and diagnostic tests are compensated for by induced savings, and the net costs are positive (+$58). Clearly, the outcomes are sensitive to assumptions about the natural history of the adenoma-carcinoma sequence.

In the variant with lower unit costs of screening, surveillance, and diagnostic tests, the total induced costs are lower than those in the expert model, resulting in increased cost savings compared with the base case. In the variant with higher screening costs, the total induced costs are almost doubled, and only 55% of the induced costs by screening, surveillance, and diagnostic tests are compensated for by the induced savings.

Discussion

The results of this study are meaningful because similar analyses of screening programs for breast and cervical cancer [de Koning 1991, van Ballegooijen 1993] have not demonstrated potential cost savings under any reasonable set of assumptions. The different results for colorectal cancer screening follow for at least two reasons. First, the cost of colorectal cancer treatment is much higher than an endoscopic procedure during which adenomas can be removed. Therefore, the potential savings for an individual in whom colorectal cancer is prevented because of endoscopy are large, in contrast with breast cancer screening where all targeted lesions are cancerous and require extensive cancer treatment. Second, the incidence of colorectal cancer is relatively high and thus the number of preventable cancers is considerable, unlike the case of cervical cancer, where the background incidence is low, at least in industrialized countries where screening is most active.

In screening, costs are induced a number of years before the potential savings in treatment. Discounting reduces the weight of future savings of preventive measures relative to the costs of the intervention. Therefore, discounted net cost savings are achieved only if the undiscounted savings are considerably larger than the costs. Endoscopic colorectal cancer screening might be one instance of secondary prevention where the 3% discounted induced savings are of the same magnitude or even larger than the induced costs. A discount rate of 3% is recommended by the Panel on Cost-Effectiveness in Health and Medicine. The net costs per person in the baseline model change to -$146 with 0% discounting and to $28 with 5% discounting.

Our analysis assumes stability of important model parameters over an extended period of time. If changes in screening test characteristics or the costs and benefits of treatment occur in the future, the economic implications of the screening policy would need to be reconsidered. If screening test characteristics improve or screening tests become cheaper, net savings would increase, while better or cheaper treatment would make screening less worthwhile. Individual health-care provider organizations might find the prospect of cost savings in the relatively distant future less compelling, especially if the cost savings are likely to be realized by a public program such as Medicare rather than the private health provider who finances screening. However, these problems of time horizon of health benefits are shared by other preventive health programs as well. Furthermore, even if colorectal cancer screening does not save costs from the perspective of private health-care provider organizations, it may still be worthwhile because the effects are likely to be large and the costs relatively small, resulting in a favorable cost-effectiveness ratio.

The results should be seen as preliminary because considerable uncertainty currently exists about the progression of precursor lesions. Better estimates of the distribution of the sojourn time of progressive adenomas and the sensitivity of endoscopic tests will be available after analysis of the results of endoscopic screening trials [Senore 1996, Berry 1997, Brevinge 1997] in coming years. Meanwhile, the assumptions in the presented model are being validated against data from other colorectal cancer screening studies, such as the Minnesota Cancer Control Study of Fecal Occult Blood screening [Mandel 1993], the Kaiser program of sigmoidoscopy screening in Northern California [Palitz 1997], and the National Polyp Study of colonoscopic surveillance [Winawer 1993a, Winawer 1993b]. The validation studies are expected to provide more information about the natural history of colorectal cancer and thus about the potential savings in treatment costs that are brought about by removal of the preceding adenoma.

The present results also depend on the relatively low unit costs of sigmoidoscopy and colonoscopy. We believe that these unit cost assumptions are plausible, especially within the context of a screening program designed to be based on dedicated screening and follow-up clinics, as in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the NCI [Gohagan 1994]. When screening is introduced on a large scale, the tests could also be delivered by mid-level health professionals [DiSario 1993]. In our baseline model, cost-saving no longer occurs at procedure costs that are double our base case, of similar magnitude to those incurred in a traditional low-volume office setting [Lewis 1999]. This result underlines the need to investigate the true cost of sigmoidoscopy and colonoscopy in organized high-volume settings [Gohagan 1994, Berry 1997, Palitz 1997]. Our results are based on an idealized screening policy with 100% screening compliance of the population. If compliance is lower, screening induces the same amount of costs and savings per screenee as in the 100% compliance model, as long as compliers do not differ systematically from noncompliers. If noncompliers occasionally comply, the balance of costs and savings is more favorable because less intensive screening results in a more favorable cost-savings balance. We have not considered the out-of-pocket and time costs incurred by individuals to undergo screening and diagnostic procedures, as recommended by Gold *et al.* [Gold 1996] or the perhaps considerable savings of such costs due to avoidance of cancer treatment for some screened individuals. Nor have we considered the costs associated with the promotion of screening. In an efficiently designed screening program, such costs should be a fraction of the costs of the initial screening procedures costs; however, there is, to date, little documented information on the actual magnitude of promotional costs for colorectal cancer screening.

The diagnostic follow-up and surveillance protocols incorporated into the expert model are consistent with the results of the National Polyp Study [Winawer 1993b] and current practice guidelines [Winawer 1997]. These are areas of continuing clinical controversy and it is likely that current practice is more aggressive than assumed in our model. However, there is little documentation of the variation in current practice. Future modeling work, taking advantage of emerging data in this area [Levin 1999], may be useful in clarifying the trade-off between economic savings and clinical risk when comparing alternative approaches to diagnostic follow-up and surveillance. We have not

attempted to determine what an optimally efficient program might be in terms of different ages of initiating and terminating screening, differential recruitment of higher risk populations, or combinations of several endoscopic screening modalities by age. More detailed modeling may possibly reveal a screening strategy that is more efficient under baseline assumptions than the one we have modeled.

The costs of colorectal cancer screening have also been assessed in other models [Eddy 1990, Lieberman 1995, Wagner 1996, Glick 1998, Gyrd-Hansen 1998, Whynes 1998], two of which assessed the costs and savings of sigmoidoscopy screening. None of these studies found negative costs of screening, and all concluded that screening may be cost-effectiveness. Our conclusions about the potential cost savings of endoscopic screening are not inconsistent with other modeling results when differences in assumptions and structure are taken into account.

According to the model of the Office of Technology Assessment of the U.S. Congress [Wagner 1996, Glick 1998], every 5-year sigmoidoscopy screenings after age 50 years generate 5% discounted net costs of $378 per screened person, assuming that only 70% of the cancers are preceded by adenomas and that the mean duration of progressive adenomas is 10 years. This amount is higher than our 3% discounted net costs estimate of $58 per person in the whole population when we assume the same percentage of cancers preceded by adenomas and the same mean duration of progressive adenomas. If we use the same discount rate of 5% and calculate the costs per person in the screening ages, our estimate is $271. Furthermore, in the Office of Technology Assessment model, more latent cancers (i.e., preclinical cancers that would never have been clinically diagnosed) are detected by screening than in our model. Lieberman [Lieberman 1995] assessed the costs of sigmoidoscopy screening at age 55 years followed by another sigmoidoscopy at age 60 years if the first screening was negative. He found net costs of this screening program of $1355 per screenee compared with $677 costs of colorectal cancer treatment without screening, resulting in $678 net costs of screening. These net costs are high compared with our estimated net costs and are explained by the high unit costs in the Lieberman model: $1000 for colonoscopy without polypectomy, $1500 with polypectomy, and $150 for screening sigmoidoscopy.

This study shows that endoscopic colorectal cancer screening has the potential to be cost saving. The preliminary results of this study support the importance of ongoing and newly initiated endoscopic screening trials.

Acknowledgement

Supported by Public Health Service contract NO1CN55186 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

We thank the participants of the working meetings held June 5-7, 1996, and May 12-13, 1997, in Bethesda, MD. We also thank Joe Selby of Kaiser-Permanente Northern-California and Tim Church of the Minnesota Colon Cancer Control Study for their contribution.

Participants in MISCAN-COLON Expert Model Meetings

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Note

SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

Appendix A. Improving the cost-effectiveness of colorectal cancer screening

In this chapter, we showed that sigmoidoscopy screening for colorectal cancer might result in net cost savings under expert-based assumptions. Although savings start to exceed costs after 22 years, it takes about 45 years for a continuing screening program to be compensated by savings before all costs. A screening program that terminates after 30 years will achieve net cost savings at 35 years after the start of the program. As Atkin *et al.* [Atkin 2000] point out, health planners tend not to be so farsighted and the technologies for treating and screening for colorectal cancer will most likely improve in future decades. Thus, the sigmoidoscopy program may be replaced by an alternative screening program within 30 years. Figure 4.3 shows what happens if the sigmoidoscopy screening program is abandoned after 10 years or 20 years. A 10-year screening program will achieve net cost savings in the 19^{th} year after the start of screening, while a 20-year screening program needs 27 years to achieve net cost savings. If a sigmoidoscopy screening were to be replaced within a decade or two by other technologies, the point where cumulative costs are completely compensated by the cumulative savings of sigmoidoscopy screening will be reached with a lag of several years. Thus, while organizations that are considering the economic implications of this kind of screening program still need to think in terms of a relatively long time horizon, this problem is perhaps less daunting than implied by our initial analysis.

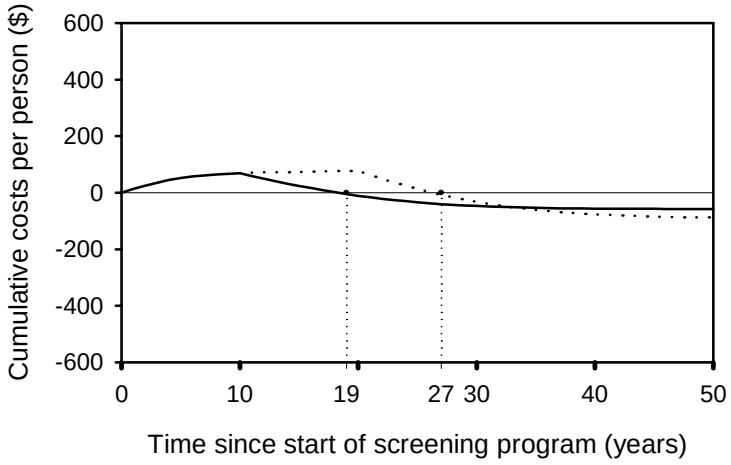

Figure 4.3 Net costs for a program of sigmoidoscopy-based colorectal cancer screening. Dotted vertical lines show number of years before induced savings equal costs. ——— = net total costs of a sigmoidoscopy screening program that terminates after 10 years. ····· = net total costs of a sigmoidoscopy screening program that terminates after 20 years.

Costs and savings can also be calculated from the private perspective of a typical U.S. health maintenance organization (HMO), assuming that around 40% of the HMO participants aged 50-75 years will no longer be enrolled within 10 years. The costs of sigmoidoscopy screening for the participants no longer enrolled in an HMO are paid by the HMO, but the savings will not accrue to the HMO. That means that sigmoidoscopy screening will probably not result in net cost savings from the perspective of the HMO. However, our model also expects favorable health effects from sigmoidoscopy screening, and the decision to screen should be based on a favorable balance between health effects and costs of screening rather than solely on a cost analysis.

5

National Polyp Study data: evidence for regression of adenomas

Abstract

Objectives

The data of the National Polyp Study, a large longitudinal study on surveillance of adenoma patients, is used for testing assumptions on the adenoma-carcinoma sequence.

Methods

The observed adenoma and colorectal cancer incidence in the National Polyp Study were compared with the simulated outcomes of the MISCAN-COLON model of epidemiology and control of colorectal cancer for the United States population based on expert opinion. Variants of this model were explored in order to identify assumptions on the adenoma-carcinoma sequence that are consistent with the study observations.

Results

The high observed adenoma detection rates at surveillance and low observed colorectal cancer incidence in the National Polyp Study could only be explained by assuming a high incidence rate of adenomas accompanied by regression of adenomas.

Conclusions

The National Polyp Study data suggest that adenoma prevalence results from a dynamic process of both formation as well as regression of adenomas. This lowers the expectations for the effects of colorectal cancer screening strategies that focus on adenoma detection.

Introduction

The evolution of colorectal cancer from a precursor lesion, the adenoma, was first reported in studies from St. Mark's Hospital in London and later designated by Morson and coworkers as the adenoma-carcinoma sequence [Morson 1976, Morson 1984]. Morson stated that the evolution of cancer from adenomas takes at least five years and may be more than 20 years [Morson 1976]. Introduction of colonoscopy provided an opportunity for clarifying this sequence because of its ability to examine the entire colon and remove polyps for pathological examination. These pathology studies have in recent years been correlated with molecular genetic studies [Vogelstein 1988]. The adenoma-carcinoma sequence is now well established as the major pathway for the development of colorectal cancer in the general population and in high risk patients in families with Familial Adenomatous Polyposis (FAP) and Hereditary Non-Polyposis Colorectal Cancer (HNPCC) [Muto 1975, Morson 1984]. The epidemiology and natural history of adenomas are not only important for choosing the optimal follow-up policy after polypectomy, but also for evaluating endoscopic screening for colorectal adenomas and cancer. A better understanding of the dynamics of the adenoma-carcinoma progression would further clarify what can be expected of various colorectal cancer screening strategies that involve adenoma detection.

The National Polyp Study was a longitudinal study that provided prospective data on the adenoma-carcinoma sequence and the effect of colonoscopic polypectomy. It was organized in 1978 and began to accrue patients in 1980. Its purpose was to evaluate more frequent and less frequent follow-up surveillance intervals in patients in whom newly diagnosed adenomas were removed. Removal of these adenomas resulted in a colorectal cancer incidence that was markedly lower than expected without polypectomy. In this report we present a study of the natural history of the adenoma-carcinoma sequence, applying a micro-simulation model for colorectal cancer epidemiology and control (MISCAN-COLON) [Loeve 1999] to the data of the National Polyp Study.

Material and methods

The National Polyp Study data

The National Polyp Study was a randomized controlled trial of colonoscopic surveillance in patients who have had at least one adenoma removed [Winawer 1993b]. All patients referred for colonoscopy or polypectomy between November 1980 and February 1990 in seven participating centers who did not have a family or personal history of familial polyposis, inflammatory bowel disease, or a personal history of polypectomy or colorectal cancer were eligible for enrollment in the study. A total of 9112 subjects referred for colonoscopy were candidates for the study. Of these, 4763 were excluded because no polyps were found. Other excluded subjects were 776 with non-adenomatous polyps only, 549 with colorectal cancer, 149 with inflammatory bowel disease or other conditions, and

35 with a sessile adenoma with a base larger than 3cm. Patients with incomplete initial examinations were also excluded (n=208). The colon had to be cleared with 3 examinations or within 3 months for the patient to be part of the study. Of the 2632 eligible patients, 1418 patients consented to participate and were randomized to one of two arms. All detected polyps were removed and a surveillance colonoscopy was offered in Arm A at 1, 3 and 6 years after initial colonoscopy and in Arm B at 3 and 6 years after initial colonoscopy. If the colon was not cleared with high confidence at surveillance colonoscopy, the patient was scheduled for repeat colonoscopy. Mean follow-up time was 5.9 years. Five cancers were found during the trial (C. I. 1.6-11.7) (2 in arm A and 3 in arm B), while 21 were expected based on the U.S. population with the same age and sex distribution [Winawer 1993a], and 43 to 48 were expected based on a comparison with two polyp bearing cohorts without intervention [Stryker 1987, Atkin 1992]. All five cancers were asymptomatic malignant adenomas detected at surveillance colonoscopy.

The model

The results of the MISCAN-COLON model are generated by micro-simulation of individuals in whom adenomas and subsequent colorectal cancer may develop. Although the MISCAN-COLON model is originally designed for evaluation of population based screening in an asymptomatic population, it can also be used to simulate surveillance after polypectomy. The output of the model consists of the adenoma and cancer detection rates at initial and surveillance colonoscopy and the effect of initial and surveillance colonoscopy on cancer incidence and mortality.

Parameter values in the expert-opinion-based model (expert MISCAN-COLON model) as presented in Table 5.1 have been established during two meetings at the United States National Cancer Institute [Loeve 1998, Loeve 1999, Loeve 2000]. In this expert model, it is assumed that adenomas are either non-progressive and will never develop into cancer in a lifetime or progressive and are destined to develop into colorectal cancer. The average duration between incidence of a progressive adenoma and clinical diagnosis of cancer is assumed to be 20 years. The duration between adenoma incidence and preclinical colorectal cancer is assumed exponentially distributed with a mean of 16.4 years, while the duration of preclinical cancer is exponentially distributed with a mean of 3.6 years. It is assumed that polypectomy completely prevents growth of the polyp into cancer.

If all individuals have equal risk for adenomas, i.e., adenomas are randomly distributed over the population, the resulting adenoma multiplicity is Poisson distributed. However, autopsy studies show a larger than Poisson variation [Koretz 1993], probably because of variation in genetic and environmental factors. The model accounts for the heterogeneity in adenoma multiplicity by drawing a risk index for each individual. The individual adenoma incidence rate is equal to the individual risk index multiplied by the age-specific adenoma incidence rate. This risk index is drawn from a gamma distribution with mean 1 and a variance of 2, which is chosen to fit the multiplicity distribution of adenomas in autopsy studies [Diggle 1994]. The probability that a new adenoma is progressive is age-dependent but does not depend on the individual risk index. The age-specific adenoma incidence and the probability that an adenoma is progressive is chosen to fit observed US cancer incidence in 1978 before the introduction of screening [National

Table 5.1 Main assumptions in the expert MISCAN-COLON model, established in expert meetings at the National Cancer Institute in 1996 and 1997.

Parameter	Value	Based on
Adenoma incidence	Age dependent: 40-49 yrs: 0.9% per yr 50-59 yrs: 1.9% per yr 60-69 yrs: 3.3% per yr 70-79 yrs: 2.6% per yr	Adenoma prevalence in autopsy and colonoscopy studies of 15% in age group 50-59 to 33% in age group 70+ [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993], cancer incidence in SEER registry in 1978 [National Cancer Institute 2001]
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 2	Multiplicity distribution of adenomas in autopsy studies [Koretz 1993]
Duration distributions in preclinical stages	Exponential	Expert opinion, other cancer models [Walter 1983, Gyrd-Hansen 1997, Launoy 1997]
Mean duration of non-progressive adenomas	Lifelong	Expert opinion
Mean duration of progressive adenomas	16.4 yrs	Expert opinion
Mean duration of preclinical cancer	3.6 yrs	Cancer detection rate at first screening and background cancer incidence in FOBT trials [Hardcastle 1989, Kronborg 1989]
Probability to develop cancer from removed adenoma	0%	Expert opinion
Sensitivity of diagnostic and surveillance colonoscopy for adenomas	≤5mm: 80% 6-9mm: 85% 10+mm: 95%	Back-to-back colonoscopy studies [Hixson 1991, Rex 1997b, Rex 1997c]
Sensitivity of diagnostic and surveillance colonoscopy for cancer	95%	Back-to-back colonoscopy studies [Hixson 1991, Rex 1997b, Rex 1997c]

Cancer Institute 2001] and prevalence of adenomas in autopsy and colonoscopy studies [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993].

The participants in the National Polyp Study had adenomas diagnosed and removed. The MISCAN-COLON model is adapted to this situation by applying a

fictitious screening test to the general population to select individuals with adenomas detected at diagnostic colonoscopy. These individuals constituted the simulated trial population. Like in the National Polyp Study, simulated individuals with colorectal cancer diagnosed at the diagnostic colonoscopy were excluded from the trial population. The sensitivity of the fictitious screening test was adjusted to reproduce the age distribution, the distribution of adenomas over the distal and proximal colon, and the size and multiplicity-distribution of adenomas at initial polypectomy in the National Polyp Study.

In the National Polyp Study, incomplete surveillance colonoscopies (%) were followed by repeat colonoscopy. Therefore, we define a surveillance examination as a series of one or more colonoscopies in a short time period of which at least one reaches the cecum and the examination is considered to be of high confidence. The reach of a surveillance examination is assumed to be 100%, i.e., the complete bowel is visualized. The reach of the initial colonoscopy is also assumed to be 100% because patients with incomplete initial colonoscopies were excluded from the study. Sensitivity of the initial colonoscopy and the surveillance examinations is based on tandem studies of colonoscopy and increases from 80% for adenomas ≤5mm to 95% for preclinical cancer [Hixson 1991, Rex 1997b, Rex 1997c]. The simulated population of 5 independent simulations of 30,000 each (5*30,000=150,000) was designed to be approximately 100 times as large as the observed National Polyp Study cohort of 1,418 patients in minimize chance variation in the simulation results. The National Polyp Study surveillance schema and the observed compliance rates per arm and round are applied to the simulated trial population.

Analysis

Outcomes of the model are the simulated number of cancers during the trial and the simulated number of surveillance examinations at which adenomas are detected. The model further differentiates between cancers that are detected by a surveillance examination and those that are interval detected. These cancers are further subdivided into those originating from adenomas or preclinical cancers missed at initial colonoscopy, and those in newly developed, fast-progressing lesions.

The observed cancer and adenoma incidence rates in the trial were compared with the rates as simulated by the MISCAN-COLON model based on expert opinion. In case of discrepancies between observed and simulated results, we varied a few pivotal assumptions in order to search for models that are consistent with observed results. Parameters that were varied are the adenoma incidence in the trial population, the duration distribution of progressive adenomas, the spontaneous regression rates of non-progressive adenomas, and the sensitivity of colonoscopy.

The goodness of fit of each set of model assumptions is evaluated by the deviance, which compares five outcomes of the model with the observed National Polyp Study results. The results that are included in the deviance are the number of surveillance detected (asymptomatic) cancers (observed in the National Polyp Study: 5), the number of interval cancers (observed: 0), the number of surveillance examinations with adenomas in Arm A at the first surveillance examination (observed: 150 in 545 examinations), in Arm A at the 2nd surveillance examination (observed: 73 in 338 examinations) and in Arm B at

the first surveillance examination (observed: 137 in 428 examinations). The deviance is defined as

$$\sum_{i=1}^{5} 2 \cdot (k_i (\log p_i - \log \lambda_i) + (n_i - k_i) \cdot (\log(1 - p_i) - \log(1 - \lambda_i)))$$

where k_i is the observed number of occurrences for outcome i, n_i is the observed number of participants for the cancer results and the number of examinations for the adenoma results, $p_i=k_i/n_i$ is the observed rate, and λ_i is the simulated rate. A low deviance indicates a good fit with the National Polyp Study data. If the deviance is higher than 11.07, the simulated results are significantly different from the observed results in the National Polyp Study.

Results

MISCAN-COLON model based on expert opinion

Table 5.2 shows that the MISCAN-COLON model based on expert opinion simulated a

Table 5.2 Characteristics at initial polypectomy of all patients and their adenomatous polyps included in the National Polyp Study, as observed in the National Polyp Study and as simulated in the expert MISCAN-COLON model (n=1418).

Characteristic	Observed	Simulated
Age		
<50	13%	11%
50-59	28%	27%
60-69	39%	40%
70-79	18%	20%
80+	2%	3%
*Adenoma size**		
≤5mm	27%	27%
6-9mm	18%	17%
≥10mm	55%	56%
*No. of adenomas**		
1	57%	61%
2	22%	23%
≥3	20%	16%
*Site of largest adenoma**		
Distal colon	64%	61%
Proximal colon	36%	39%

* Forty-four patients with polyps classified as adenomas by the local pathologist were classified as non-adenomas by the review pathologists and were excluded from the National Polyp Study cohort simulated in this modeling study (n=1374).

cohort that successfully reproduced the characteristics at initial polypectomy of the National Polyp Study population. However, this expert MISCAN-COLON model simulates a cancer incidence during the surveillance period of 1.5 per 1000 person-years which is more than twice as high as the observed 0.6 (95% confidence interval 0.2-1.4), while it simulates a 18% adenoma detection rate at surveillance examinations which is considerably lower than the observed 27% (95% confidence interval, 25%-30%), see model A in Table 5.3. Of the simulated cancer incidence in the first six years after initial polypectomy, 61% is caused by cancers developed from new progressive adenomas, 22% is caused by missed adenomas that progressed into cancer and 18% is from preclinical cancers missed at initial colonoscopy. Of the simulated cancers, 40% is found at surveillance colonoscopy, and 60% are diagnosed because of symptoms, while in the National Polyp Study all 5 incident cancers were detected at surveillance. The overall goodness of fit of the expert model is poor, mainly caused by the poor fit of adenoma detection rates.

Natural history assumptions to better explain the observed rates

Higher model-simulated adenoma detection rates than in the expert MISCAN-COLON model can be achieved with a lower sensitivity of colonoscopy for adenomas or a higher adenoma incidence.

Low sensitivity for adenomas. The sensitivity for adenomas has to be extremely low in order to simulate the observed adenoma detection rates in the National Polyp Study, which conflicts with the low observed cancer incidence (model B in Table 5.3).

Higher adenoma incidence. The simulated adenoma detection rates are more in agreement with the observations when the adenoma incidence rate in the patients referred for colonoscopy is doubled (model C in Table 5.3). The resulting adenoma prevalence is not in agreement anymore with the adenoma prevalence in the unscreened general population which is about 33% in the 70+ age category [Johnson 1990, DiSario 1991, Lieberman 1991b, Rex 1991, Koretz 1993, Levin 1999]. However, the National Polyp Study cohort is a selected population with an adenoma incidence that may be higher than in the general population. A serious problem is that increasing the adenoma incidence also increases the risk for cancers, thus further increasing the already too high simulated cancer incidence (from 1.5 to 2.4 per 1000 person years compared to 0.6 observed). This could theoretically be resolved by restricting the increase in incidence to non-progressive adenomas. However, this would make the cancer risk in patients with multiple adenomas similar to the cancer risk in patients with only one adenoma, which is not consistent with published data that show that adenoma multiplicity is a risk factor for colorectal cancer [Lotfi 1986, Bertario 1999]. Therefore, assuming a higher adenoma incidence that is associated with a higher adenoma prevalence has to be rejected.

Higher adenoma incidence combined with regression. The high adenoma detection rates in the National Polyp Study can also be explained by assuming high adenoma incidence compensated by spontaneous regression of (non-progressive) adenomas. If spontaneous regression occurs regularly, adenoma incidence can be high while adenoma prevalence agrees with observed prevalence, even in older age groups where adenoma prevalence and multiplicity hardly increase according to autopsy and colonoscopy studies.

Table 5.3 Cancer incidence rate and proportion of surveillance examinations with adenomas as observed in the National Polyp Study population and as simulated with the expert MISCAN-COLON model and several model variants.

	Cancer rate per 1000 person years			Proportion of surveillance examinations with adenomas				
	Surveillance detected	Interval detected	All	Arm A, year 1	Arm A, year 3	Arm B, year 3	All	Deviance
Observed	**0.6**	**0.0**	**0.6***	**0.28**	**0.22**	**0.32**	**0.27****	
A. Expert MISCAN-COLON assumptions	0.6	0.9	1.5	0.17	0.13	0.25	0.18	84
Assumptions intended to raise the adenoma detection rate								
B. Low adenoma sensitivity (60%)	1.3	1.7	2.9	0.28	0.19	0.31	0.27	32
C. High adenoma incidence	1.0	1.4	2.4	0.26	0.21	0.36	0.28	28
D. High adenoma incidence and spontaneous regression	0.5	0.7	1.1	0.21	0.25	0.34	0.26	24
Assumptions intended to reduce the cancer incidence rate								
E. No fast-growing adenomas (constant duration of 20 yr)	0.3	0.3	0.6	0.16	0.11	0.23	0.17	104
F. High cancer sensitivity (100%)	0.5	0.7	1.2	0.17	0.12	0.24	0.18	83
Assumptions intended to fit both the cancer incidence and adenoma detection rate								
G. No fast-growing adenomas, high adenoma incidence and spontaneous regression	0.2	0.2	0.4	0.21	0.26	0.35	0.27	27
H. High cancer sensitivity, high adenoma incidence and spontaneous regression	0.4	0.6	1.0	0.22	0.25	0.34	0.26	23

* 95% Confidence interval 0.2-1.4

** 95% Confidence interval 0.25-0.30

Although it is generally assumed that adenomas grow into cancer or remain in the colon until death, spontaneous regression or washout of adenomas has been reported [Cole 1961, Knoernschild 1963, Hoff 1986, Giardiello 1993]. In the observational study of Knoernschild, the mucosa near asymptomatic benign polyps was tattooed in 257 patients. After follow-up of 3 to 5 years, the polyp had completely disappeared in 18% of the patients. Table 5.3 shows the results of model D in which non-progressive adenomas disappear on average after 5 years with an exponentially distributed duration. The adenoma incidence is three to five times higher than in the expert MISCAN-COLON model. Between the ages 55 years and 84 years the incidence is approximately 10% per

year with a peak in age group 70-74 years of 16% per year. This model variant results in adenoma detection rates that are more in agreement with the National Polyp Study observations. Because in this model most individuals will develop adenomas at some time during their life, the colorectal cancer risk in individuals with adenomas is less increased than in the expert MISCAN-COLON model. This explains why the simulated colorectal cancer incidence is lower than in the expert MISCAN-COLON and not significantly different from the observed colorectal cancer incidence (model D in Table 5.3).

In summary, a high adenoma incidence combined with spontaneous regression of adenomas is the only explanation of the observed adenoma detection rate that does not increase simulated cancer incidence and even decreases the simulated cancer incidence. The deviances of models B, C, and D are all lower than the deviance of the expert MISCAN-COLON model, which indicates that models B, C, and D are more in agreement with the National Polyp Study results. The simulated results of model B and C are still significantly different from the observed results ($P<0.05$), mainly due to the difference in interval-detected cancers. The simulated results of model D are significantly different from the observed results ($P<0.05$), due to the difference in interval-detected cancers and the simulated adenoma detection rate in Arm A, year 1.

To decrease the simulated cancer incidence further, we explored two possibilities for lowering the cancer incidence: no fast-growing progressive adenomas, and a high sensitivity of colonoscopy for cancer.

No fast-growing adenomas. In the expert MISCAN-COLON model, approximately 30% of the progressive adenomas will develop into cancer within six years, due to the exponentially distributed duration of 20 years on average. With fewer fast-growing progressive adenomas than assumed in the expert MISCAN-COLON model, cancers from new polyps will not surface in the first years after polypectomy and thus the incidence will remain low. As an example, model E in Table 5.3 is a model in which adenomas do not develop into cancer within the trial period, i.e., there are no fast-growing (within six years) progressive adenomas. Under these assumptions, none of the incident cancers in the first six years after polypectomy are newly developed, 74% develop from cancers missed at initial colonoscopy and 26% develop from adenomas missed at initial colonoscopy. The percentage of cancers developing from missed adenomas is small, because most missed adenomas are small and take more than six years to develop. In this simulation, 51% of the cancers are diagnosed at surveillance examinations, compared to 39% in the expert model. The simulated cancer incidence rate decreases from 1.5 to 0.6 per 1000 years, which is equal to the observed rate.

Higher sensitivity for cancer. The assumed sensitivity of colonoscopy for cancer is 95% in the expert model, based on a retrospective study of colonoscopic sensitivity for cancer [Rex 1997c]. However, in the NPS study sigmoidoscopy or barium enema was performed as the reason for referral for colonoscopy in 25% and 44% of the patients respectively [Winawer 1992] and often additional colonoscopies were performed to "resolve" cases, which gives extra opportunities to detect cancer in these patients. Raising the sensitivity for preclinical cancer in the MISCAN-COLON model from 95% to 100%

reduces the incidence from missed cancers. But because missed cancers cause only 18% of the cancer cases in the expert model, the decrease in cancer incidence is modest, from 1.5 to 1.2 per 1000 years (model F in Table 5.3).

Neither of these two assumptions that increase the cancer incidence in the study period affect the simulated adenoma detection rates, which remains too low. Because the deviance largely depends on the adenoma detection rates, the deviances of model E and F are comparable or higher than the expert MISCAN-COLON model (model A).

Table 5.3 shows the results of the MISCAN-COLON model with high adenoma incidence and spontaneous adenoma regression, combined with no fast-growing progressive adenomas (model G), and combined with 100% colonoscopic sensitivity for cancer (model H). The simulated cancer incidence in model G is more than 60% reduced compared to model F, while the simulated cancer incidence in model H is only slightly reduced compared to model F. In Model D the simulated cancer incidence is higher than observed, but not significantly different. If that model is modified with the assumption of no fast growing adenomas (model G), the simulated cancer incidence is lower than observed, but again not significantly different. Thus, models that include the assumption of development and regression of adenomas and in which the percentage of the progressive adenomas that will develop into cancer within six years is between 0% and 30% are consistent with the observed cancer incidence. The deviances of model G and H are comparable with the deviance of model D.

Discussion

The assumptions of the expert MISCAN-COLON model were developed in collaboration with the National Cancer Institute, United States, in meetings of a group of colorectal cancer experts [Loeve 1999]. In order to clarify the natural history of the adenoma-carcinoma sequence, a few pivotal natural history assumptions made by this group were modified to determine which natural history assumptions best fit the National Polyp Study observed data. The expert MISCAN-COLON model predicted a higher cancer incidence and lower adenoma detection rates than observed in the National Polyp Study. In order to have the highest concordance between the model results and the National Polyp Study results, a new factor had to be introduced, i.e., adenoma regression.

High adenoma incidence combined with regression accounted for the high percentage of patients with adenomas at surveillance, without losing its consistency with adenoma prevalence data from autopsy studies and without increasing the colorectal cancer incidence during the study. The high incidence is supported by a study of repeat colonoscopy that estimated that the 1-year adenoma incidence rate is 11% [Bensen 1999]. The assumption that adenomas spontaneously regress is supported by previous findings in short-term studies that adenomas may regress in size [Hoff 1986, Hofstad 1996]. A recent study of celecoxib in patients with familial adenomatous polyposis reported adenoma regression in the control group. In this study, a tattoo was placed at baseline endoscopy near a small area with a high density of polyps. Repeat endoscopy was performed six months later and the number of polyps at the tattooed area in the placebo group was 4.5%

less than at baseline endoscopy [Steinbach 2000]. The Telemark study recently reported that adenoma prevalence in patients who had undergone sigmoidoscopy 13 years before was not significantly lower than in the patient without previous sigmoidoscopy. The authors mention adenoma regression as one of the possible explanations [Thiis-Evensen 2001].

The cost-effectiveness of repeat sigmoidoscopy or colonoscopy colorectal cancer screening in the general population has been studied using models [Frazier 2000, Khandker 2000, Sonnenberg 2000]. None of these included the assumption that adenomas regress and adenoma incidence is accordingly high. High adenoma incidence combined with regression makes adenoma detection as a strategy for colorectal cancer prevention less favorable, because more adenomas will develop in the population after polypectomy. Furthermore, it is likely that more individuals will develop at least one adenoma. Thus, in repeat screening rounds, many adenomas will be detected in those without previous adenomas. There is less difference in risk level between individuals with and without adenomas, making surveillance of adenoma patients less effective. Also, many adenomas will be detected at surveillance in individuals with adenomas detected, as observed in the National Polyp Study. This increases the financial and quality of life costs expected of frequent surveillance and (endoscopic) screening.

The National Polyp Study provided the opportunity to examine the dynamics of the natural history of the adenoma-carcinoma sequence. The outcome suggests that the adenoma-carcinoma sequence is a dynamic process of formation and regression of adenomas. This has negative consequences for the effects and costs expected from endoscopic colorectal cancer screening and surveillance of adenoma patients.

Acknowledgement

Work was partially supported by Research Contract NO1-CN-55186 with the National Cancer Institute in Bethesda, Maryland. Support was also given by the Tavel-Reznik Fund. The authors thank Martin Brown, Project Officer of the National Cancer Institute.

6

Colorectal cancer risk after colonoscopic polypectomy

Abstract

Background

Adenoma patients are generally advised to have surveillance after polypectomy. The surveillance schedule should depend on the colorectal cancer risk after initial polypectomy.

Aims

To estimate the relative colorectal cancer risk in the first years after colonoscopic polypectomy compared with the age- and sex-matched general population.

Patients

553 consecutive adenoma patients whose initially detected adenomas were colonoscopically removed in the endoscopy department of the Slotervaart Hospital, a general hospital in Amsterdam, the Netherlands. Colonoscopic surveillance was offered to the patients.

Methods

Colorectal cancer incidence was studied in these 553 adenoma patients. A literature search was performed to identify all studies on relative colorectal cancer risk after polypectomy.

Results

The colorectal cancer relative risk in the patients from the Slotervaart Hospital was 0.9 (0.3-2.0). Five other studies on colorectal cancer relative risk after colonoscopic polypectomy were identified by the literature search. Two studies that excluded patients with large sessile polyps published relative risk estimates of 0.2 (0.1-0.6) and 0.3 (0.1-0.7). Relative risk estimates in the three studies that included patients with large sessile polyps were 0.7 (0.2-1.4), 0.8 (0.2-2.3) and 1.3 (0.6-2.3). In all studies patients were offered regular colonoscopic surveillance.

Conclusions

The present review shows that the colorectal cancer risk in the first years after colonoscopic polypectomy in adenoma patients does not exceed the colorectal cancer risk in the general population. The results support the lengthening of the surveillance interval to 5 years for most adenoma patients.

Introduction

Colorectal cancer is a major cause of morbidity and mortality in developed countries. The estimated number of new colorectal cancer cases for the United States in 2002 is 148,300 and 56,600 deaths from colorectal cancer are expected [American Cancer Society 2002]. It is generally believed that the majority of cancers originate from adenomas. It is therefore recommended that adenoma patients undergo initial complete colonoscopy in order to detect and remove all adenomas. However, some adenomas are missed at the initial colonoscopy, and new adenomas may develop at significant rates. Therefore, patients in whom adenomas are removed are recommended to be surveilled regularly by colonoscopy with an interval of 3 or 6 years, while less intensive screening strategies is recommended for the general population. Surveillance should not be performed too frequently, because colonoscopies are expensive and involve complication risks. The optimal surveillance interval depends amongst others on the colorectal cancer risk in adenoma patients after initial polypectomy. There is a wide variation in published relative colorectal cancer risk estimates. In the National Polyp Study, the colorectal cancer risk in the first six years after adenoma removal was only 0.2 of the risk in the general population [Winawer 1993a]. Contrarily, the colorectal cancer risk in the Funen adenoma surveillance trial was 1.3 of the risk in the Danish normal population [Jørgensen 1993]. The aim of the present study is to estimate the relative colorectal cancer risk in the first years after colonoscopic polypectomy compared with the age- and sex-matched general population. It is explored whether differences in estimated relative colorectal cancer risk are explained by differences in inclusion criteria and in which way surveillance guidelines deal with these criteria. This is estimated from primary data provided by the endoscopy department of the Slotervaart hospital, Amsterdam, the Netherlands, and from a literature search to identify all other studies concerning relative colorectal cancer risk in the first years after colonoscopic polypectomy. Surveillance was performed in all studies and the effect of surveillance on colorectal cancer risk is explored.

Material and Methods

Cohort study in the Slotervaart hospital

Data of all 553 patients diagnosed with adenomas between 1988 and 1998 in the Slotervaart hospital, a general hospital in Amsterdam, the Netherlands, were collected. The date of birth, gender, and reason for the first visit (incomplete) were recorded. Data collected for each colon examination were date of the examination, examination method (colonoscopy, sigmoidoscopy, and barium enema), reach of the scope, and the result of the examination. The number of adenomas and the site of the adenomas were not systematically recorded. Date and results of the examinations recorded in the endoscopy department were matched with the pathology reports of these patients in the Pathological Anatomical Nation-wide Automated Archive (Palga). The histology of the adenomas was

not always recorded in these pathology reports. Patients were included in the present study if an adenoma was registered in the Palga registry at the time of the first colon examination at the endoscopy department. Several colon examinations within a week, for example a barium enema and a sigmoidoscopy examination, were considered to be one examination in this study. Patients were excluded if they had a diagnosed colorectal carcinoma before or within 7 days after the initial examination, and if they had a diagnosis of inflammatory bowel disease. Patients were followed until 1 October 1998 for the occurrence of colorectal cancer. The patient record was examined for all patients in whom colorectal cancer was diagnosed more than 7 days after the initial examination according to the pathology reports to decide whether or not it was a metachronous cancer.

Follow-up time was calculated as the time between the initial examination registered at the endoscopy department and 1 October 1998. Calculation of expected number of colorectal cancers is based on site-, sex- and age-specific colorectal cancer incidence rates in general population of the Netherlands in 1995 multiplied by the observed number of person years at risk [Visser 1998]. The ratio of observed to expected cases is reported as a rate ratio. 95% Confidence intervals are based on the exact Poisson distribution and are calculated using STATA 7.0.

Literature search

A literature search was performed to find all publications in which colorectal cancer incidence after colonoscopic polypectomy in adenoma patients is compared with colorectal cancer incidence in the general population. A literature search was performed in PubMed database of the National Library of Medicine in October 2002 to find all publications with the following Medline headings: “colorectal neoplasms” and “colonoscopy” and either “adenoma” or “adenomatous polyps” or “colonic polyps”. Moreover, the Medline subheading “surgery” was added to the search to identify articles concerning polypectomy. The search resulted in 115 selected articles. The titles and abstracts of the publications were scanned and publications containing primary data on colorectal cancer incidence in adenoma patients after colonoscopic polypectomy were considered for inclusion. Publications that did not compare the cancer incidence in adenoma patients with the background incidence in the age- and sex-matched general population were excluded. 95% Confidence intervals are based on the exact Poisson distribution and are calculated using STATA 7.0.

Results

Retrospective cohort study in the Slotervaart hospital

Table 6.1 shows the characteristics of the 553 adenoma patients from the Slotervaart Hospital at the initial colon examination with polypectomy. The patients were regular referrals from the Amsterdam West sector with approximately 375,000 inhabitants. Mean age at the initial examination was 62.1 years. In most patients (77%) the reason for colonoscopy was unknown. These were usually patients with symptoms who had a sigmoidoscopy and who were referred to colonoscopy due to the detection of adenomas.

Table 6.1 Patients and adenoma characteristics in present study at initial examination (n=553).

Characteristic	Number (%) of patients	
Age at initial polypectomy		
<50	91	(16)
50-59	120	(22)
60-69	191	(35)
70-79	136	(25)
80+	15	(3)
Sex		
Male	292	(53)
Female	261	(47)
Reason for referral		
Family history	62	(11)
Symptoms	8	(1)
Polyp at sigmoidoscopy	23	(4)
Earlier adenoma	33	(6)
Unknown	427	(77)
Histology of adenoma with highest grade of abnormality		
Tubular	195	(35)
Tubulovillous	199	(36)
Villous	20	(4)
Carcinoma in situ	10	(2)
Unknown	129	(23)

Screening in average-risk asymptomatic individuals was not performed at the time in the Netherlands. Mean follow-up time of the adenoma patients was 5.3 years and the mean number of colonic examinations, including the initial examination was 2.2. 66% of the patients had at least one surveillance examination, 35% had at least two surveillance examinations, and 15% had three or more surveillance examinations. Surveillance was stopped before the end date of the study in 86 patients (16%), mostly due to their age. 93% of the initial and 84% of the surveillance examinations were performed with colonoscopy. Otherwise, a combination of barium enema and sigmoidoscopy was generally performed. The cecum was reached in 94% of the initial colonoscopies and in 91% of the surveillance colonoscopies. 22% of the surveillance examinations occurred within a year since the previous examination, 40% occurred in the second year, and 12% in the third year since the previous examination. Adenomas were found in 24% of the surveillance examinations.

Five colorectal cancers were diagnosed during the follow-up period. Table 6.2 shows characteristics of these patients. The number of adenomas removed at the initial examination was not known for all patients, but was retrieved for the cancer cases. Patient 1 had asked for screening at the age of 57 years because of a family history of colorectal cancer. The initial colonoscopy did not reach the ascending colon and cecum. A radiological examination was performed shortly afterwards at which no lesions were detected. A metastasized tumor was diagnosed in the cecum two years later. In Patient 2,

adenomas were diagnosed at the age of 56 years. The patient had a surveillance colonoscopy one year later at which only hyperplastic polyps were diagnosed. Two years later a Dukes' C carcinoma was diagnosed in this patient at another hospital. Patient 3 had an initial colonoscopic examination at the age of 77 years. One year later, a sigmoidoscopy was performed at which no additional adenomas were detected. The next surveillance colonoscopy one year later was incomplete and did not reach the ascending colon and the cecum. One tubulovillous adenoma was removed at this surveillance colonoscopy. Surveillance was stopped at the age of 79 years due to the patient's age. At the age of 83 a tubulovillous adenoma containing a Dukes' A adenocarcinoma in the ascending colon was diagnosed at another hospital. Patient 4 had an initial colonoscopic examination at the age of 77 years at which tubular adenomas were removed and at the surveillance colonoscopy one year later two tubular adenomas were removed. Thereafter, surveillance was stopped due to the age of the patient. At the age of 85, a Dukes' A adenocarcinoma in the rectum was detected at another hospital. Patient 5 had two tubulovillous adenomas removed at the age of 70 years. A sigmoidoscopy was performed one year later at which no additional adenomas were detected. Two years after this examination, a polyp containing a Dukes' A adenocarcinoma was detected in the sigmoid. None of the cancers were detected at surveillance. One carcinoma was registered in the period between the initial examination and the first surveillance examination.

Table 6.2 Characteristics of colorectal cancer cases in present study. TV=tubulovillous adenoma; T=tubular adenoma.

Patient no.	1	2	3	4	5
Sex	Male	Male	Female	Male	Male
Age at cancer diagnosis (yr.)	59	60	83	85	73
Histology of adenomas at initial examination	Unknown	TV	Unknown	T	TV
Number of adenomas removed at initial examination	4	2	3	7	2
Number of examinations after initial examination	0	1	2	1	1
Time between initial examination and cancer diagnosis (yr.)	2.0	3.4	6.0	8.3	2.9
Time between last examination and cancer diagnosis (yr.)	2.0	1.9	4.1	6.9	2.0
Anatomical site of cancer	Cecum	Cecum	Ascending colon	Rectum	Sigmoid
Dukes' stage	D	C	A	A	A

Colorectal cancer incidence in adenoma patients during the complete follow-up period was 0.86 (0.3-2.0) of the expected incidence in the general population (n=5). Colorectal cancer incidence in adenoma patients between the initial examination and first surveillance examination was 0.43 (0.0-2.4) of the expected incidence in the general population with the same age and sex distribution (n=1). The relative risk compared to the general population in 70 patients who had an incomplete examination was 1.2(0.0-6.5) (n=1). The relative risk compared to the general population in 483 patients with complete initial colonoscopies was 0.8 (0.2-2.1) (n=4). The relative risk compared to the general population in the 62 patients with a family history of colorectal cancer was 4.4 (0.1-24.6) (n=1).

Literature search

The literature search identified five other studies that published estimates of the relative colorectal cancer risk after initial colonoscopic polypectomy compared with the rate in the general population, see Table 6.3. The studies are described below. The aim of the National Polyp Study was to evaluate the effect of surveillance in adenoma patients [Winawer 1993a, Winawer 1993b]. Patients were excluded if they had a family or personal history of familial polyposis, inflammatory bowel disease, or a personal history of polypectomy or colorectal cancer. A total of 9112 subjects referred for colonoscopy were candidates for the study. Patients were excluded if colonoscopy detected no polyps, non-adenomatous polyps only, colorectal cancer or a sessile adenoma with a base larger

Table 6.3 Reported colorectal cancer incidence in patients in whom adenomas were removed and relative colorectal cancer risk compared with the age- and sex-matched general population.

Study	No. patients	Patients with sessile polyps included	Mean follow-up time (yr.)	Person years	No. cases	Relative risk (95% CI)
National Polyp Study [Winawer 1993a, Winawer 1993b]	1418	No	5.9	8401	5	0.2 (0.1-0.6)*
Citarda *et al.* [Citarda 2001]	1693	No	10.5	14211**	6**	0.3 (0.1-0.7)**
Lund *et al.* [Lund 2001]	776	Yes	6.6	5138	6	0.7 (0.2-1.4)***
Meagher *et al.* [Meagher 1994]	645	Yes	4.4	2847	3	0.8 (0.2-2.3)
Funen Adenoma Surveillance Study [Jørgensen 1993]	1056	Yes	4.3	not published	10	1.3 (0.6-2.3)
Cohort study in Slotervaart hospital	553	Yes	5.3	2924	5	0.9 (0.3-2.0)

* relative risk is 0.3 (0.1-0.8) if the first 2 years of follow-up are excluded

** excluding the first 2 years of follow-up

*** relative risk is 0.4 (0.1-1.1) if two malignant polyps are excluded

than 3cm. The 1418 adenoma patients who entered the study had had a complete initial colonoscopy at which all detected polyps were removed. A surveillance colonoscopy was offered in Arm A at 1, 3, and 6 years after initial colonoscopy, and in Arm B at 3, and 6 years after initial colonoscopy. Mean follow-up time was 5.9 years. Five colorectal cancers were found during the trial (2 in arm A and 3 in arm B), the relative colorectal cancer risk compared to the general population being 0.2 (0.1-0.6).

Citarda *et al.* [Citarda 2001] studied 1693 patients enrolled between 1980 and 1987 who had had at least one adenoma larger than 5mm in diameter removed at the initial examination that consisted of complete colonoscopy or (incomplete) colonoscopy and double contrast enema. Data were collected from seven reference centers for gastrointestinal disease and neoplasms in Italy. Patients with genetic syndromes, previous adenomas or colorectal cancer, previous colonic resection, inflammatory bowel disease or sessile adenomas more than 3cm in diameter were excluded. Follow up ended by a total colon examination or telephone interview. The mean number of follow-up years was 10.5 years. The surveillance strategy in these patients was not reported, but 74% of the patients had a colonoscopy in the last four years of the study. The relative colorectal cancer risk compared to the general population excluding the first two years after initial examination was 0.3 (0.1-0.7). Three colorectal cancers diagnosed within 2 years after the initial examination were excluded.

Lund *et al.* [Lund 2001] studied colorectal cancer incidence in 776 patients who underwent colonoscopy for the following reasons: colorectal symptoms, possible polyp or other findings on barium enema, or positive fecal occult blood test detected in the Nottingham screening trial. The initial examination consisted of complete colonoscopy or (incomplete) colonoscopy and a barium enema. Six months after the initial examination a further sigmoidoscopy was performed. Patients were randomized to surveillance by flexible sigmoidoscopy or colonoscopy at varying intervals. Follow-up was until March 1998 for patients in the Nottingham fecal occult blood screening study and for patients not in this study total follow-up was until the last visit within the surveillance study. They found a relative colorectal cancer risk compared to the general population of 0.4 (0.1-1.1). However, two malignant Dukes' A polyps were not considered invasive cancer in that study that would have been defined as colorectal cancer in all other studies. This increases the relative risk compared to the general population to 0.7 (0.2-1.4).

Meagher *et al.* [Meagher 1994] reviewed records of all patients who underwent colonoscopic polypectomy by a single surgeon between 1974 and 1991 in Australia. Patients with colorectal cancer, inflammatory bowel disease, familial adenomatous polyposis were excluded. There were 645 patients who underwent removal of at least one adenoma and had at least one surveillance colonoscopic examination. Patients were followed until their most recent colonoscopic examination for a mean of 4.4 years. During the follow-up period, 3 patients developed cancer, while 3.75 were expected in the general population, the relative risk being 0.8 (0.2-2.3).

The Funen adenoma surveillance study followed 1056 patients for the occurrence of adenomas [Jørgensen 1993]. The initial colonoscopy consisted of complete colonoscopy in 1027 patients, 19 patients had incomplete colonoscopy and barium enema

and 10 patients had an incomplete colonoscopy only. Patients were randomized to surveillance intervals varying from 6 to 48 months. Most surveillance examinations were performed by colonoscopy. The rate ratio in the Funen adenoma surveillance study was 1.3 (0.6-2.3).

The percentage of colorectal cancers detected at surveillance varies widely among the studies, from 100% in the National Polyp Study and the study of Meagher *et al.*, approximately 50% in the studies in Funen, of Citarda *et al.*, and Lund *et al.*, to 0% in the study in the Slotervaart hospital.

The results of the studies presented above are not combined into one estimate for the relative colorectal cancer risk after colonoscopic polypectomy, because the studies differ in design and protocol. The National Polyp Study and the study of Citarda *et al.* excluded patients with large (≥3cm) sessile adenomas and found low colorectal cancer relative risk estimates of 0.2 (0.1-0.6) and 0.3 (0.1-0.7). The relative risk estimates compared to the general population in studies that included patients with large sessile polyps was 0.7 (0.2-1.4) in the study of Lund *et al.*, 0.8 (0.2-2.3) in the study of Meagher *et al.* and 1.3 (0.6-2.3) in the Funen adenoma surveillance study. The total number of colorectal cancers observed in the studies that included large sessile adenomas, including the study in the Slotervaart hospital, was 24 where 27 cancers were expected in the general population, a relative risk of 0.9. The overlap in confidence interval of the studies that included large sessile adenomas is 0.6-1.4.

Discussion

Adenoma patients are considered to be at high risk for colorectal cancer, because adenomas are precursors of colorectal cancer. Therefore, once detected, an adenoma is removed, colonoscopy is performed and patients are regularly surveilled by colonoscopy. Meanwhile, the colorectal cancer risk in adenoma patients after removal of adenomas is not well known. The follow-up study in the Slotervaart hospital shows a relative colorectal cancer risk after colonoscopic polypectomy of 0.9 (0.3-2.0) compared to the general population. A literature search identified five other studies concerning the relative colorectal cancer risk in adenoma patients. The relative risk ranged from 0.2 (0.1-0.6) in the National Polyp Study to 1.3 (0.6-2.3) in the Funen adenoma surveillance study.

The National Polyp Study and the study of Citarda *et al.*, which excluded patients with large sessile polyps at initial examination, found low colorectal cancer relative risk estimates of 0.2 (0.1-0.6) and 0.3 (0.1-0.7). The relative risk estimates in studies that included patients with large sessile polyps ranged from 0.7 (0.2-1.4) in the study of Lund *et al.* to 1.3 (0.6-2.3) in the Funen adenoma surveillance study. This comparison suggests that large-sessile-polyp patients are at high risk for colorectal cancer, even after polypectomy. This stresses the importance of studying the colorectal cancer incidence in these patients in all reviewed studies. None of the studies reported the cancer incidence in large-sessile-polyp patients. In the Slotervaart study, none of the cancers were diagnosed in these patients. Studying incidence in large-sessile-polyp patients may explain differences between studies and may result in detailed surveillance guidelines for these

patients. The present updated guidelines of the American Gastroenterological Association state that patients with a large sessile adenoma should have a shorter surveillance interval than other adenoma patients based on clinical judgement [Winawer 2003].

Besides the in- or exclusion of patients with large sessile polyps, other factors may contribute to differences in reported colorectal cancer risk. Firstly, the completeness of the initial and follow-up examinations may have influenced the reported colorectal cancer risk. As an example, in the Slotervaart study, the initial colonoscopy had not visualized the cecum in Patient 1. Although the initial colonoscopy was followed by barium enema, a carcinoma was diagnosed in the cecum two years later. Patient 3 had had initial complete colonoscopy, followed by a follow-up sigmoidoscopy and incomplete follow-up colonoscopy. Four years later, cancer was diagnosed in the ascending colon. It is possible that the cancer incidence in this study would have been lower if incomplete colonoscopies had systematically been followed by repeat colonoscopy. For example, in the National Polyp Study, an initial or follow-up colonoscopy was repeated if the gastroenterologist was not confident that all polyps had been cleared.

Secondly, the follow-up strategy in older adenoma patients may have affected cancer incidence. In the Slotervaart study, two cancers were diagnosed in patients (Patient 3 and Patient 4) who had stopped follow-up several years before diagnosis due to their high age (>75 yr.). These two Dukes' A cancers may have been prevented if these patients had continued follow-up. In the reviewed studies, follow-up was not stopped in older patients. If the two cancers in the Slotervaart study would have been prevented, the relative colorectal cancer risk would decrease to 0.52 (0.1-1.5).

In all reviewed studies, the study population was subjected to surveillance. Surveillance decreases colorectal cancer incidence after a certain time period. On the other hand, colorectal cancer incidence increases at the moment of surveillance by detection of asymptomatic cancers. A modeling study showed that it takes approximately 6 years before the cumulative incidence is reduced [Zauber 2000]. Therefore, given the short follow-up time of the studies, surveillance may have raised rather than decreased the cancer incidence.

The wide variation in the percentage of colorectal cancers detected at surveillance (asymptomatic cancers) and not by symptoms among the studies can be explained by the small number of cancer cases per study. Furthermore, the percentage asymptomatic cancers is correlated with the average number of surveillance examinations per patient. In the Slotervaart hospital 0% (n=5) of the cancers were detected at surveillance and the average number of surveillance examinations was 1.2. The Lund study had 1.5 surveillance examinations (mainly sigmoidoscopy) and 33% (n=6) of the cancers were detected at surveillance. The Funen study had 3.1 surveillance examinations per patient and 60% (n=10) of the cancers were detected at surveillance. In the National Polyp Study, 100% (n=5) of the cancers were surveillance-detected. The National Polyp Study patients had on average 1.2 surveillance examinations, but some of them consisted of several colonoscopies, because colonoscopy was repeated if the first colonoscopy was incomplete. The Citarda study and the Meagher study did not publish the number of surveillance examinations performed during the study.

In the updated guidelines of the American Gastroenterological Association, the surveillance interval for patients with 1 or 2 small (<1cm) adenomas was lengthened from 3 to 5 years [Winawer 2003]. Lengthening is supported by the present result that adenoma patients with no large sessile polyps are at lower colorectal cancer risk than the general population in the first years after polypectomy. The results of the review do not rule out that the surveillance interval can also be extended for other patients, such as patients with large adenomas, or patients with 3 or more adenomas. This could be confirmed by a trial. Any conclusions about surveillance intervals longer than 5-6 years cannot be drawn from the reviewed studies, because the studies only report the colorectal cancer risk in the first years after polypectomy.

The present review shows that the colorectal cancer risk in the first years after colonoscopic polypectomy in adenoma patients (including those with large sessile polyps) does not exceed the colorectal cancer risk in the general population. It is suggested that the risk for patients with non-sessile adenomas is lower than in the general population. The results support lengthening of the surveillance interval to 5 years in recent guidelines for adenoma patients with 1 or 2 small adenomas.

Acknowledgement

We would like to thank N. de Vries for data entry, and E. Riemersma, T. Limarno, and L. van der Meer of the endoscopy department, Slotervaart Hospital, Amsterdam, and dr. Westerga and G. Scholte of the pathology department, Slotervaart Hospital, Amsterdam for their assistance.

7

Colorectal cancer risk in adenoma patients: a nation-wide study

Abstract

Introduction

Colorectal cancer incidence after adenoma removal has been studied in selected populations of adenoma patients. The present study estimates the trend in colorectal cancer incidence after adenoma removal in actual clinical practice.

Material and Methods

From PALGA, a nation-wide network and registry of histo- and cytopathology in the Netherlands, we extracted data of all patients diagnosed with colorectal adenomas between 1 January 1988 and 1 October 1998. The data were used to calculate population-based colorectal cancer incidence rates after adenoma removal.

Results

A total of 78,473 adenoma patients were followed for a mean of 4.5 years after the first adenoma removal. The colorectal cancer incidence ratio compared with the general population matched by age and sex was 38.4 (37.3-39.5) in the first year after adenoma removal and 1.5 (95% CI, 1.4-1.6) after the first year. The incidence ratio decreased from 2.8 (2.5-3.1) in the second year to 0.9 (0.6-1.2) in year 9-11. This time trend is the opposite of the upward time trend that was expected after adenoma removal.

Conclusions

Adenoma patients in the Netherlands are at increased risk for colorectal cancer compared to the general population. The high cancer incidence in year 1-5 after polypectomy can be explained by a colonoscopic sensitivity for cancer of approximately 90%.

Introduction

Adenomas are considered to be precursors of colorectal cancer and are effectively removed by endoscopy. A complete initial colonoscopy with polypectomy is recommended in individuals with adenomas because they are at increased risk for colorectal cancer. Furthermore, colonoscopic surveillance is recommended in these individuals in order to detect missed and newly developed adenomas and asymptomatic cancer. Several studies in selected centers and selected adenoma patients reported on the colorectal cancer incidence in the first years after adenoma removal. The incidence ratio compared with the general population ranged from 0.2 in the National Polyp Study [Winawer 1993a], and 0.4 in the study of Lund *et al*. [Lund 2001] to 1.3 in the Funen study [Jørgensen 1993]. Patients in these studies had undergone complete initial colonoscopy or incomplete initial colonoscopy followed by (negative) barium enema. In the National Polyp Study, patients with large sessile polyps were excluded from the analysis. In unselected adenoma patients, the incidence ratio after adenoma removal may be higher than in these studies, because the compliance with and the quality of the initial colonoscopy and colonoscopic surveillance is lower than in the selected centers and because patients with large sessile polyps are included.

The studies published to date have been too small to study the trend in colorectal cancer incidence according to time since polypectomy. However, the expectation was that the effect of polypectomy would decline over time. In the first years after polypectomy, colorectal cancer incidence was expected to be low. It was thought that the incidence would later gradually increase to the level of the incidence in adenoma patients who had not previously undergone polypectomy.

The aim of the present study was to estimate the colorectal cancer incidence ratio in actual clinical practice in a large unselected population of adenoma patients. A further aim was to investigate the trend in incidence ratio according to time since first adenoma removal. To this end, we investigated the incidence of colorectal cancer in all 78,473 patients who were diagnosed with adenomas in the period from 1 January 1988 to 1 October 1998 in the Netherlands.

Material and Methods

All Dutch pathology laboratories are connected to the PALGA, a nation-wide network and registry of histo- and cytopathology. The last laboratory was connected in 1990. This registry contains 99% of all pathology reports in the Netherlands. Patients in this registry are identified by date of birth, sex, and the first 4 characters of their family name. All pathology reports on colorectal tissue in the observation period between 1 January 1988 and 1 October 1998 were retrieved. The following items were made available for each report: sex, date of birth, date of pathology review, conclusion text and diagnostic code [Stichting PALGA 1999]. The diagnostic code is based on the Systematized NOmenclature of MEDicine (SNOMED) issued by the College of American Pathologists.

It contains a topological term and a morphology term describing the finding, e.g. “colon*villous adenoma”. The SNOMED morphology codes are identical to the codes in the International Classification of Diseases for Oncology (ICD-O-2; World Health Organization) [World Health Organization 1990]. The SNOMED codes that were used to classify a lesion as an adenoma, a carcinoma in situ or colorectal cancer are described in Appendix A. The date of first adenoma removal was defined as the date of first adenoma diagnosis or diagnosis of carcinoma in situ in the observation period. It was unknown whether these adenomas were removed or only biopsied and whether the adenomas were located in the proximal or distal colon.

The SNOMED codes for colorectal cancer used in this study are identical to the codes used by the Netherlands Cancer Registry to classify histological results as colorectal cancer. The colorectal cancer definition used and the retrieval from PALGA was checked by comparing the resulting number of new colorectal cancer cases in 1995, which was 7985, to the number of histologically confirmed colorectal cancer cases reported in the national cancer registry, which was 7993 [Visser 1998]. In young age groups, the number of cancer cases differed, but the numbers were small. In the 55-59 age group, the number of cancer cases was 630 according to the definition, while the national cancer registry reported 599 cases (difference: 5.2%). In the 5-year age groups between 60 and 79 years, the difference in colorectal cancer cases was <2%.

During the period of observation, adenomas were found in 101,290 individuals. The results are based on 78,473 of these individuals who had no bowel disease or resection of the bowel at the date of first adenoma removal. Thus, patients with colorectal cancer (n=8188) or a resection of the colorectal tract (n=100) before or at the date of the first adenoma removal were excluded. Furthermore, patients recorded in the pathology report as having inflammatory bowel disease (n=10,484), polyposis coli (n=406), and hereditary bowel disease (n=54) were excluded from the analysis. Patients with a lesion that was classified as “suspect” at the date of first adenoma removal (n=3585) were also excluded from the analysis, as these were mainly expected to be suspected malignancies. This was confirmed by the high number of colorectal cancers detected in these patients (incidence rate 560 per 1000 person years).

Adenoma patients were followed up in the registry from the date on which they underwent adenoma removal for the first time to 1 October 1998 for the occurrence of colorectal cancer or a diagnosis of metastases of colorectal cancer in other sites. Follow-up was stopped if a non-colorectal cancer in the colorectal tract, such as lymphoma, was diagnosed, if metastases of a primary cancer in another site of the body were found in the colorectal tract, or if (partial) resection of the colorectal tract was performed for other reasons. Calculation of the expected number of cancers was based on sex- and age-specific colorectal cancer incidence rates in the general population of the Netherlands in 1993 [Visser 1996] multiplied by the observed sex- and age-specific number of person-years at risk. The ratio of observed to expected cases is reported as a standardized incidence ratio. 95% confidence intervals are reported between brackets, based on the exact Poisson distribution and are calculated using STATA 7.0.

Results

The results are based on 78,473 patients registered as having undergone adenoma removal in the period between 1 January 1988 and 1 October 1998. Table 7.1 shows the age and sex distribution of the patients undergoing initial adenoma removal during the period of this study. The adenoma diagnosis rate in the population of the Netherlands during the study period was 51 per 100,000 person years, increasing from 10 per 100,000 person years in individuals aged <50 years to 232 per 100,000 person years in individuals aged 70-79 years. Although the prevalence of adenomas is known to climb with age, this increase also reflects the (unknown) frequency of endoscopy according to age and possible calendar time. The mean age of patients undergoing adenoma removal for the first time was 64.9 years and the mean number of follow-up years after first adenoma removal was 4.5 years.

Figure 7.1 shows the colorectal cancer incidence rate by time interval since the first adenoma, and the expected incidence in the general population with the same age and sex distribution. During follow-up, 5949 colorectal cancers were diagnosed. In the year immediately following diagnosis of the first adenoma, 5002 colorectal cancers were

Table 7.1 Age and sex of the 78,473 adenoma patients included in the study with first adenoma removal in the period 1 October 1988-1 October 1998.

Characteristic	Percentage	(No.)
Sex		
Male	54	(42,294)
Female	46	(36,179)
Age group		
<50 yr.	14	(10,664)
50-59 yr.	19	(15,026)
60-69 yr.	29	(22,608)
70-79 yr.	27	(21,275)
80+ yr.	11	(8,900)

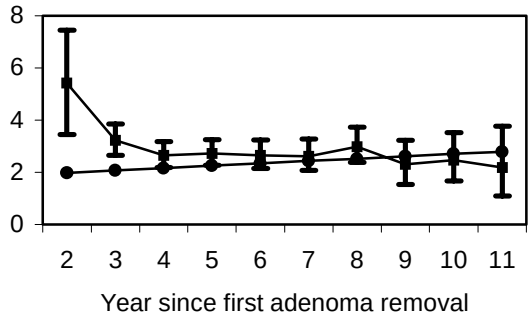

Figure 7.1 Observed colorectal cancer incidence per 1000 person years more than one year after first adenoma removal (■) and incidence rate expected in the sex- and age-matched general population (●). Observed colorectal cancer incidence in the first year after adenoma removal was 72 per 1000 person years.

diagnosed, which corresponded to a very high cancer incidence of 72 per 1000 person years and a standardized incidence ratio of 38.4 (37.3-39.5). In the second year, 327 colorectal cancers were diagnosed and the incidence dropped to 5.4 per 1000 person-years. In later years, the incidence declined somewhat over time, from 3.2 per 1000 person years in year 3 to 2.2 in year 11. The standardized incidence ratio declined from 2.8 (2.5-3.1) in the second year after initial polypectomy to 0.9 (0.6-1.2) in year 9-11 after the first adenoma removal.

Table 7.2 Standardized incidence ratio (SIR) of colorectal cancer after first adenoma removal.

Follow-up time	SIR
All	7.9 (7.7-8.1)
>3 months after first adenoma removal	2.1 (2.0-2.2)
>12 months after first adenoma removal	1.5 (1.4-1.6)
>24 months after first adenoma removal	1.2 (1.1-1.3)
>60 months after first adenoma removal	1.1 (0.9-1.2)

Some patients will be diagnosed with colorectal cancer very shortly after the initial adenoma removal, due to the adenoma being detected during the process of diagnosing cancer. Table 7.2 shows the standardized incidence ratio of colorectal cancer on exclusion of a certain period immediately following initial adenoma removal. The incidence ratio was 7.9 (7.7-8.1) when taking the total follow-up period into account, but was found to decrease to 1.5 (1.4-1.6) on exclusion of the first year, and to 1.1 (0.9-1.2) if the first 5 years after first adenoma removal are excluded. Between 5 and 11 years after undergoing adenoma removal for the first time, therefore, the colorectal cancer risk is comparable to that of the general population. In the remainder of this section, results are presented excluding the first year after first adenoma removal.

In Table 7.3, colorectal cancer incidence is stratified by age, sex, histology, and site of the first adenoma. The incidence of colorectal cancer increased with age (from 1.1 in ages <50 years to 4.1 in ages 80+ years), as expected, but the incidence ratio compared with the general population decreased with age (from 4.0 in ages <50 years to 1.1 in ages 80+ years). This age trend may be explained by the hypothesis that in young age groups, most colonoscopies are performed in individuals with a familial colorectal cancer risk or with symptoms. There were no significant differences in standardized incidence ratio according to pathology of the first adenoma. The standardized incidence ratio was smallest among patients with tubular adenomas and highest among patients with villous adenomas. The 1135 patients with carcinoma in situ had a standardized incidence ratio comparable with the patients with tubular adenomas.

The number of preventive colonoscopies probably increased between 1988 and 1998. This could explain the lower standardized incidence ratio in patients diagnosed with adenomas in the period 1992-1996 (in follow-up year 2 and 3 after first adenoma removal) compared with patients diagnosed with adenomas in 1988-1992 (1.9 versus 2.4, see Table 7.3).

Table 7.3 Colorectal cancer incidence and standardized incidence ratio (SIR) in 64,699 adenoma patients excluding the first year after first adenoma removal.

Characteristic	Incidence per 1000 person-years (cases)	SIR (95% CI)
All	3.4 (947)	1.5 (1.4-1.6)
Sex		
Male	3.3 (503)	1.3 (1.2-1.5)
Female	3.4 (444)	1.8 (1.6-1.9)
Age at first adenoma removal		
<50	1.1 (44)	4.0 (2.9-5.4)
50-59	2.8 (152)	2.7 (2.3-3.1)
60-69	3.6 (296)	1.6 (1.4-1.8)
70-79	4.4 (330)	1.3 (1.1-1.4)
80+	4.1 (125)	1.1 (0.9-1.3)
Pathology of most advanced adenoma at first adenoma removal		
Carcinoma in situ	3.6 (17)	1.4 (0.8-2.2)
Villous adenoma	5.3 (84)	2.1 (1.7-2.6)
Tubulovillous adenoma	3.5 (194)	1.6 (1.3-2.6)
Tubular adenoma	2.9 (217)	1.4 (1.2-1.5)
Adenoma, histology unknown	3.3 (435)	1.5 (1.4-1.7)
Site of first adenoma		
Rectum	4.0 (253)	1.8 (1.6-2.1)
Colon	3.1 (679)	1.4 (1.3-1.5)
Colon and rectum	3.8 (15)	1.6 (0.9-2.6)
*Date of first adenoma removal**		
1 October 1988-1 October 1992	4.9 (262)	2.4 (2.1-2.7)
1 October 1992-1 October 1996	3.8 (209)	1.9 (1.7-2.2)

* Results based on colorectal cancer cases and person years in year 2 and 3 after first adenoma removal.

In the pathology registry, individuals were identified by an identification code consisting of the date of birth, sex, and the first 4 characters of their family name. This code was not 100% unique: individuals with the same date of birth, sex, and first 4 characters of their family name were registered under a single identification code. In addition to the identification code, each pathology report was also marked with the patient's first initial, birthplace and place of residence The results were corrected for colorectal cancer cases incorrectly assigned to adenoma patients, by calculating the incidence ratio in adenoma patients to whom cancers were solely assigned if these additional identifying fields were identical in the pathology reports. According to these calculations, the standardized incidence ratio excluding the first year after first adenoma removal was 1.3 (95% CI, 1.2-1.4), declining from 2.5 (2.2-2.8) in the second year to 0.8 (0.6-1.1) in year 9-11. The incidence ratio in the first year was 37.7 (36.6-38.7). Thus, if

the results are corrected for identification problems, the trend in incidence ratio is still present, although the estimated incidence ratios slightly decrease.

Discussion

This study provides an estimate of the colorectal cancer incidence in a nation-wide population of patients after endoscopic removal of a first adenoma. The study shows that, with the current polypectomy and surveillance practice, adenoma patients have a significantly higher risk for colorectal cancer than the general population, as evidenced by the incidence ratio of 1.5 (1.4-1.6) on excluding the year immediately following initial adenoma removal. The standardized incidence ratio declined from 2.8 (2.5-3.1) in the second year to 0.9 (0.6-1.2) in year 9-11 after adenoma removal was first performed.

This unexpected downward time trend in cancer incidence following initial adenoma removal was also observed by Levi *et al.*, the only other population-based study published until now [Levi 1993]. The authors of this study followed a group of Swiss patients for a mean of 4.1 years after removal of a first adenoma. They reported a colorectal cancer incidence ratio of 3.1 in month 4-12 after polypectomy, declining to an incidence ratio of 1.8 thereafter without any further time trend.

An explanation for the downward incidence trend may be that the high incidence in the first years after polypectomy is mainly caused by cancers missed at the first adenoma removal in patients with cancer-related symptoms. Since, in the clinical situation, all patients with suspected colorectal cancer undergo endoscopy, the missed cases in the present data all relate to individuals in the total population with symptomatic colorectal cancer and synchronous adenomas. Examining the colorectal cancers diagnosed within a period of three months before to three months after initial adenoma removal, we found that a total of 8393 colorectal cancers were diagnosed “at” the initial adenoma diagnosis. During 5 years of follow-up (excluding the first 3 months), 1289 colorectal cancers were detected. On the basis of these figures, we were able to arrive at an 87% sensitivity of colonoscopy for colorectal cancer. Some of the 1289 cancers will have been new cases that were not present as cancers at the first adenoma removal. Using the MISCAN-COLON model [Loeve 1999], we estimated that approximately 230 of the cancer cases occurring between year 1-5 were new. The sensitivity estimate adjusted for these new cancer cases is 90%. This estimate agrees with the results of studies on colonoscopic sensitivity for cancer or large adenomas [Hixson 1991, Rex 1997b, Rex 1997c], which supports the hypothesis that the high incidence in year 1-5 after polypectomy is mainly caused by cancers missed at the initial adenoma removal. Not performing a second colonoscopy in adenoma patients with persistent symptoms can obviously result in delayed diagnosis and high colorectal cancer incidence that is not limited to the first year after polypectomy.

The adenoma patients without (missed) colorectal cancer at the initial colonoscopy were comprised of those who were screened because of a family history of colorectal cancer, as well as patients with symptoms not caused by colorectal adenoma or cancer. A low incidence of cancer was expected in these patients in the first years after adenoma

removal because of their having no (missed) cancer at baseline and having been screened and treated for colorectal cancer precursors: adenomas. An increase in colorectal cancer incidence was expected in later years because of new, progressive disease developing in these higher (than average) risk patients.

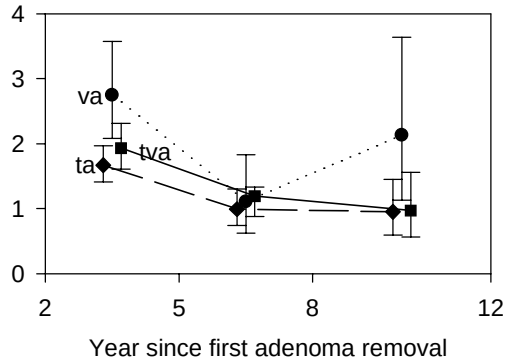

Figure 7.2 Observed colorectal cancer incidence ratio after first adenoma diagnosis according to pathology at first adenoma diagnosis: tubular adenomas (ta), tubulovillous adenomas (tva) and villous adenomas (va).

In summary, the patients with symptoms related to colorectal cancer govern the observed colorectal cancer incidence in the first years, and the patients without colorectal cancer related symptoms govern in later years. In order to investigate this hypothesis further, we calculated the observed time trend in incidence ratio separately for patients with tubular, tubulovillous, or villous adenomas (Figure 7.2). Patients with a carcinoma in situ or an adenoma with unknown histology were not included in the figure. Colorectal cancer incidence was expected to be high throughout the first years after the adenoma diagnosis, after which this would decrease and then once again increase in later years. As not only patients with missed cancer, but also patients at high risk for colorectal cancer in later years are more likely to have villous adenomas than other patients, this incidence trend was expected to be the most pronounced in patients with villous adenomas. Indeed, a high incidence was seen in patients with villous adenomas in years 2-3, presumably due to cancers missed at the first adenoma removal. By years 5-7, most missed cancers had shown up and the incidence ratio was relatively low. According to the point estimates, the incidence rate will once again start to rise in years 8-11 due to newly developed cancers. The hypothesis that two separate phenomena in two separate types of patients play a role is supported by the biphasic shape of the curve in patients with villous adenoma. Moreover, this shape is more pronounced for these patients compared to patients with tubular adenomas, while the results for patients with tubulovillous adenomas are intermediate.

Is the incidence of colorectal cancer after polypectomy affected by colonoscopic surveillance? Surveillance reduces the increase in incidence in later years in the second group of adenoma patients. Figure 7.3 shows the effect of the initial polypectomy alone and combined with surveillance colonoscopies on the colorectal cancer incidence in the National Polyp Study as estimated by the MISCAN-COLON expert model [Zauber 2000]. A major reduction in incidence results from the initial polypectomy. The model further predicts that with surveillance, the incidence will rise in the third year after the initial

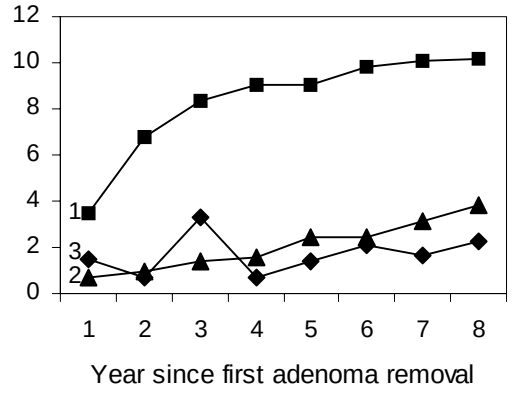

Figure 7.3 Estimated colorectal cancer incidence in adenoma patients according to the expert MISCAN-COLON model: with no initial polypectomy or surveillance (1); with initial polypectomy only (2); with initial polypectomy and surveillance (3). Age distribution and size distribution of first adenomas as in the National Polyp Study [Winawer 1993a, Winawer 1993b, Zauber 2000].

polypectomy, due to detection of asymptomatic cancer at the 3-yearly surveillance colonoscopy. However, by the sixth year after initial polypectomy, the number of colorectal cancers prevented will have compensated this increase. Thus, surveillance cannot explain the time trend in the first years after polypectomy, but may explain the absence of an increase in incidence ratio in the latter years of the present study.

Until now, most estimated incidences of colorectal cancer in adenoma patients have been based on prospective studies in selected adenoma patients with complete initial colonoscopy, polypectomy and regular surveillance in selected medical centers. The incidence ratio in these studies compared with the general population ranged from 0.2 (0.1-0.6) in the National Polyp Study [Winawer 1993a], and 0.4 (0.1-1.1) in the study of Lund *et al*. [Lund 2001] to 1.3 (0.6-2.3) in the Funen study [Jørgensen 1993]. All ratios included the first year after adenoma removal. This compares to 2.1 (2.0-2.2) in the present study (excluding the first three months after adenoma removal). Citarda *et al.* recently conducted a retrospective study in adenoma patients at seven reference centers for gastrointestinal diseases and neoplasms, in which the colorectal cancer incidence ratio was 0.3 (0.1-0.7) excluding the first two years after adenoma removal. This compares to an incidence ratio of 1.2 (1.1-1.3) in the present study. It may well be possible that many patients with symptoms related to cancer or large adenomas were excluded from these studies. Moreover, the study populations were too small and follow-up time too short to study the time trend in colorectal cancer incidence after adenoma removal.

Differences in selection criteria based on patient characteristics or the completeness of the initial examination of adenoma patients may partly cause the high incidence ratio in the present study compared to the studies mentioned. We only excluded patients with a registered history of colorectal cancer, a colonic resection, patients with registered inflammatory bowel disease, polyposis coli and other hereditary bowel disease. We had no information on gastrointestinal symptoms. In the other studies, clinical information was available and “unresolved” cases, e.g. with persistent symptoms, may not have been included. Moreover, in the National Polyp Study and the study of Citarda *et al.*, patients with sessile adenomas larger than 3cm were excluded, a proportion of whom may

have developed colorectal cancer. If these patients had been included, the colorectal cancer incidence ratio after adenoma removal may have increased to 1 or higher compared with the general population.

The National Polyp Study only included patients in whom the initial colonoscopy was complete and regarding whom the colonoscopist felt confident that the colon had been successfully cleared. In the Lund study, a barium enema was performed if the initial colonoscopy was not completed to the cecum; six months after the initial examination, a further flexible sigmoidoscopy was performed to ensure a clean left colon. In the Funen study, complete colonoscopy was attempted at the initial examination to ensure a clean colon. Barium enema was added if colonoscopy was incomplete. In patients with multiple polyps or unsatisfactory bowel preparation, colonoscopy was repeated within three months. The Citarda study only included patients with complete initial colonoscopy or partial initial colonoscopy and double contrast barium enema. It is unknown how often only a sigmoidoscopy was performed at the initial examination in the present nation-wide study, although the 1988 Dutch guidelines recommended complete initial colonoscopy with removal of all identified polyps. This may partly explain the high colorectal cancer incidence ratio in the present study. It indicates that it is important that surveillance guidelines clearly state that patients in whom adenomas are detected should undergo a complete colonoscopy. Many guidelines for surveillance of adenoma patients have been published over the past few years [Hoff 1996a, Winawer 1997, American Society for Gastrointestinal Endoscopy 2000, Nagengast 2001, Smith 2002], but most guidelines do not provide recommendations for the initial examination.

A case-control study can be performed in the present adenoma patient population in order to test our explanation of the high colorectal cancer incidence seen in the first years after the initial adenoma removal and to investigate possible improvements in patient treatment that will result in lower colorectal cancer incidence rates in the first years after adenoma removal. Cases should be individuals diagnosed with colorectal cancer within a short period after the first adenoma removal, e.g. in the second and third year, and controls should be comprised of individuals with no diagnosis of colorectal cancer and the same follow-up time. The symptoms at the initial examination, the number and quality of colonic examinations performed in these patients and the size, shape, and pathology of the initial adenomas may differ between the cases and controls. The results of the case-control study may confirm or reject the hypothesis that the high colorectal cancer incidence in the years immediately following initial adenoma removal occurs in adenoma patients with persistent symptoms. The results of such a case-control study may also lead to modified clinical guidelines, such as a recommendation to perform a second colonoscopy shortly after the initial colonoscopy in adenoma patients with persistent otherwise unexplained symptoms.

In conclusion, adenoma patients in the Netherlands are at increased risk for colorectal cancer, especially in the first years after first adenoma removal. In this study, the colorectal cancer incidence after polypectomy decreased with time since polypectomy, while an increase was expected. It is hypothesized that cancers missed during the diagnostic process cause the high cancer incidence in the first years after polypectomy,

even until the fifth year after adenoma removal. This is supported by the fact that the results are consistent with a colonoscopic sensitivity for cancer of approximately 90%. Confirmation of this hypothesis by further studies may lead to modified clinical guidelines.

Acknowledgement

The authors thank R. Kamps and M. Casparie, Stichting Palga, Utrecht and E. van den Akker-van Marle, Department of Public Health, Erasmus MC, University Medical Center, The Netherlands, for their assistance in the preparation of this manuscript. We would like to thank K. Gribling-Laird for her grammatical advice.

Appendix A. SNOMED codes used in the analysis

All SNOMED codes in the Palga registry are listed in [Stichting PALGA 1999].

SNOMED codes classified as adenoma

A T-code of format T68… or T67… combined with an M-code of format: M74000, M74006, M74007, M74008, M74009, M74850, M81400, M81401, M82100, M82110, M82210, M82600, M82611, M82630, M90100, M90130, M90140.

SNOMED codes classified as carcinoma in situ

A T-code of format T68… or T67… combined with an M-code of format: M80102, M80105, M81402, M81405, M82632.

SNOMED codes classified as rectal cancer

A T-code of format T68… combined with an M-code of format: M8…3, M8…9, M9…3, M8…9 and the first four digits of the M-code in the range:
8000-8004,8010-8012,8020-8022,8030-8035,8050-8052,8070-8075,
8140,8144,8200-8201,8210-8211,8220-8221,8230-8231,8240-8246,
8260-8263,8480-8481,8490,8560,8570-8573,8720-8722,8730,8743,
8770-8772,8775,8800,8890-8891,8894-8896,9140,9590-9593,9595,
9670-9673,9675,9677,9680-9682,9684-9688,9690-9691,9693-9695,
9697-9698,9702-9705,9711-9716,9723,9750,9990.

SNOMED-codes classified as colon cancer

A T-code of format T67… combined with an M-code of format: M8…3, M8…9, M9…3, M8…9 and the first four digits of the M-code in the range:
8000-8004,8010-8012,8020-8022,8030-8035,8140,8144,8200-8201,
8210-8211,8220-8221,8230-8231,8240-8246,8260-8263,8480-8481,
8490,8800,8890-8891,8894-8896,9140,9590-9593,9595,9670-9673,
9675,9677,9680-9682,9684-9688,9690-9691,9693-9695,9697-9698,
9702-9705,9711-9716,9723,9750,9990.

8

Discussion and recommendations

This chapter starts with the answers to the research questions as formulated in Chapter 1. Subsequently, several topics are discussed in more detail. The chapter ends with conclusions and recommendations.

Answers to research questions

In the introduction to this thesis, four research questions were formulated, the answers to which are summarized below. Some answers refer to the discussion later in this chapter.

What is the impact of systematic negative results on the colorectal cancer mortality reduction achieved by FOBT screening?

Systematic false-negative test results strongly impact on FOBT screening, if the screens are performed annually. The impact of systematic false-negative test results is much smaller in the case of biennial screening. It is unlikely that systematic negative test results played an important role in the Minnesota Colon Cancer Control Study (Chapter 3 and Chapter 8).

Are the costs of sigmoidoscopy screening compensated by induced savings?

It may well be that, in the United States, the induced savings as a result of sigmoidoscopic colorectal cancer screening completely compensate the costs thereof. This is not the case in the Netherlands. Whether the savings are able to compensate the costs mainly depends on ratio of the unit cost of sigmoidoscopy to that of colorectal cancer treatment (Chapter 4 and Chapter 8).

What natural history assumptions best explain the National Polyp Study results?
The National Polyp Study data strongly suggest that adenoma prevalence results from a dynamic process of formation and regression of adenomas (Chapter 5).

What is the colorectal cancer risk in patients with removed adenomas in the first years after polypectomy?

The colorectal cancer risk in the first years after colonoscopic polypectomy in selected adenoma patients who undergo high-quality initial colonoscopy and polypectomy and regular surveillance does not exceed the colorectal cancer risk in the general population. It is suggested that the risk in patients with non-sessile adenomas is lower than in the general population (Chapter 6). With the current polypectomy and surveillance practice in the Netherlands, adenoma patients have a significantly higher risk for colorectal cancer than the general population (Chapter 7).

The MISCAN-COLON model for the evaluation of colorectal cancer screening

Use of the MISCAN-COLON model in public health decision-making

In this thesis, use was made of the MISCAN-COLON model to calculate the costs and savings of sigmoidoscopy screening and to quantify the impact of systematic false-negative test results on the effect of FOBT screening. The model was subsequently used to study the adenoma-carcinoma sequence from the National Polyp Study data. The MISCAN-COLON model is a comprehensive model that allows for a wide variety of assumptions. It may also be used for studying problems that do not require complex modeling. This was illustrated in Chapter 3, where a simplified model was used to study the impact of systematic negative test results on the effectiveness of FOBT screening. That model did not include adenoma stages and featured only one preclinical colorectal cancer stage.

Since its development in 1996, the model has been extended to include more options for surveillance. This was necessary in order to be able to calculate the costs and effects of surveillance strategies in the project, on the basis of which the Dutch guidelines for surveillance after adenoma removal [Kwaliteitsinstituut voor de gezondheidszorg CBO 2002] were to be revised. In addition, this enabled the results obtained with this model to be compared to the findings of the National Polyp Study, which are presented in Chapter 5. In the extended MISCAN-COLON model, the surveillance interval and surveillance test could optionally be dependent on the stage of the most advanced adenoma detected at the last test, the number of adenomas detected at the last test, the age at the last test, and/or the previous surveillance interval.

Up until now, the expert MISCAN-COLON model has been used to calculate the costs and savings of sigmoidoscopy screening, as shown in Chapter 4 and the costs and effects of surveillance in adenoma patients [Kwaliteitsinstituut voor de gezondheidszorg CBO 2002]. Furthermore, assumptions were explored using the MISCAN-COLON model that could serve to explain the findings of the National Polyp Study. In the present chapter, the costs and savings of sigmoidoscopy screening are estimated using a model that is in agreement with the National Polyp Study data.

The MISCAN-COLON model is currently being used to study the possibilities for a screening trial in the Netherlands and to calculate the impact of such a trial on endoscopic capacity. It may therefore be concluded that the MISCAN-COLON model offers a useful tool for the analysis of screening and surveillance studies and for the evaluation of screening strategies. We plan to perform a cost-effectiveness analysis of colorectal cancer screening strategies after more empirical studies have been analyzed with the MISCAN-COLON model and compared to the results of the National Polyp Study analysis. The analysis of these studies will be performed according to the same procedure as was used to analyze the results of the NPS.

Table 8.1 Assumptions about the adenoma dwell time and the percentage of cancers that arise from adenomas in models used to estimate the costs and/or effects of endoscopic screening.

Model	Adenoma dwell time*	% cancers from adenomas
Expert MISCAN-COLON model	16.4 yr. for progressive adenomas, exponentially distributed	100%
[Vijan 2001]	10 yr.	75%
[Khandker 2000]	n.a.	100%
[Frazier 2000]	Annual transition probabilities: low-risk adenoma to high risk ad.: 0.02 high-risk adenoma to localized cancer: 0.05	100%
[Eddy 1990]	7 yr.	93%
[Ness 2000]	Slow-progressing: 52 yr. Fast-progressing: 26 yr.	100%
OTA model [Wagner 1996]	10 yr.	70%
[Geul 1997]	n.a.	100%

* Time between onset of adenoma and preclinical cancer

Other models in the field of colorectal cancer screening

One of the next steps will be the comparison of the MISCAN-COLON model with other models for cost-effectiveness analysis of colorectal cancer screening [Eddy 1990, Lieberman 1995, Neilson 1995, Wagner 1996, Geul 1997, Frazier 2000, Khandker 2000, Ness 2000, Sonnenberg 2000, Vijan 2001]. This will provide more insight into the difference between the models and highlight the points on which the models disagree.

We compared the assumptions about the duration of the adenoma-carcinoma sequence and the percentage of cancers developing from adenomas, which largely determine the effect of endoscopic screening. Table 8.1 shows these assumptions in models that have been used to estimate the costs and/or effects of endoscopic screening. For some models, the assumed duration of the adenoma-carcinoma sequence was not clear. The assumed duration varies between 7 years in the model of Eddy [Eddy 1990] to a mix of 26 and 52 years in the model developed by Ness [Ness 2000]. The assumed percentage of cancers arising from adenomas varies from 70% to 100%. In conclusion, the variation in assumptions about the duration of the adenoma-carcinoma sequence and the percentage of cancers preceded by adenomas is wide. The Cisnet model profiler of the Cancer Intervention and Surveillance modeling NETwork (Cisnet) funded by the National Cancer Institute in the United States can facilitate a systematic comparison of all assumptions. The primary aims of the Cisnet program are to determine the impact of cancer control interventions, such as primary prevention, screening and treatment, on observed trends in incidence and mortality and to determine whether recommended interventions are having their expected population impact. The MISCAN-COLON model and the Frazier model [Frazier 2000] will be the first two models on colorectal cancer interventions that will be compared using the model profiler.

Two models that focus on adenoma growth have been published recently [Pinsky 2000, Wilson 2001]. The Pinsky model assumes that adenoma growth is caused by a mutation of the APC gene [Pinsky 2000]. The model is intended to understand the natural history of the adenoma-carcinoma sequence. Adenoma development is modeled by stage-specific cell birth and death rates. The model concentrates on adenoma development and does not incorporate the development of colorectal cancer. The model developed by Wilson simulates colorectal cancer incidence in individuals who had a screening colonoscopy at an age between 50 and 59 years at which all detected adenomas were removed [Wilson 2001]. The model is not intended to estimate the effect of screening, but is intended to estimate the effect of non-steroid anti-inflammatory drugs (NSAIDs) on the development of adenomas and cancer and the consequences for appropriate surveillance intervals in adenoma patients. The growth rates of adenomas in the model are based on studies in which patients with unresected polyps were followed for a period of three years [Hofstad 1996]. Surveillance of adenoma patients was not modeled.

The natural history of the adenoma-carcinoma sequence and analysis of empirical studies with the MISCAN-COLON model

Main natural history parameters in the MISCAN-COLON model

The importance of parameters depends on the application of the MISCAN-COLON model. If the model is used to evaluate FOBT screening, important parameters are the duration distribution of preclinical cancer, the test sensitivity of FOBT for cancer, and the impact of early detection and treatment of cancer on prognosis. If the model is used to evaluate endoscopic screening or surveillance, important parameters are the duration distribution of adenomas, the test sensitivity of sigmoidoscopy and colonoscopy for adenomas. We wish to use the model to evaluate FOBT screening, endoscopic screening and colonoscopic surveillance, which means that all of the above parameters are essential. An important parameter about which uncertainty presently reigns is the duration distribution of progressive adenomas. If the majority of adenomas take only a few years to develop, the effect of endoscopic screening will last only a few years and the screening interval should be short. If, on the other hand, adenomas develop only slowly, the effect of endoscopic screening will be much longer lasting.

Empirical studies analyzed until now

In Chapter 5, we compared simulated results of the expert MISCAN-COLON model with the observed results in the National Polyp Study in order to investigate what natural history assumptions could explain the National Polyp Study results. The conclusion was that adenoma prevalence results from a dynamic process of both formation and regression of adenomas. The impact of these assumptions on the costs and savings of sigmoidoscopy screening are explored later in this chapter.

We compared the expert MISCAN-COLON model with data from the Minnesota Colon Cancer Control Study in order to estimate the test sensitivity of FOBT for colorectal cancer and the duration distribution of the preclinical colorectal cancer stages

[Loeve 1998]. The Minnesota study is a large randomized controlled trial of FOBT screening, with more than 10 years follow-up after the start of the study. Both rehydrated and unrehydrated FOBT tests were used. We concluded that we could not explain the Minnesota study results if we assumed that the test sensitivity was constant during the entire preclinical cancer period. We could only explain the Minnesota study results by assuming that sensitivity of FOBT for preclinical cancer is low shortly after onset of malignancy and high shortly before clinical diagnosis. Furthermore, we are currently collaborating with investigators of the COlon CAncer Prevention (CoCaP) sigmoidoscopy program and the Health Professionals' Follow-up Study to estimate the duration distribution of adenomas and the test sensitivity of sigmoidoscopy and colonoscopy for adenomas. To this end, observed and simulated colorectal cancer incidence after endoscopic screening is compared [Palitz 1997, Kavanagh 1998]. A recently funded Cisnet project proposes to extend the comparison of MISCAN-COLON results with the National Polyp Study by also modeling advanced adenomas (adenomas of size ≥1cm, villous histology, or high-grade dysplasia). Advanced adenomas are important markers of progression in the adenoma-carcinoma sequence. This will enhance the precision of the natural history assumptions in the MISCAN-COLON model.

Finally, we checked the assumption that the mean duration of preclinical cancer is 3.6 years. This assumption was based on the difference between the screen-detection rate and the background incidence in two FOBT trials [Hardcastle 1989, Kronborg 1989]. The assumption was checked by calculating the percentage of patients with unsuspected cancers in autopsy studies performed in Western countries [Eide 1978, Rickert 1979, Williams 1982b, Bombi 1988]. The duration of preclinical cancer can be estimated by dividing this percentage by the background incidence of colorectal cancer in these patients. However, the percentage of patients with unsuspected cancer ranged from 2.5% in an autopsy study in Great Britain [Williams 1982a] to 0% in an autopsy study in Spain [Bombi 1988]. This exercise was unable to provide a more precise estimate for the duration of preclinical cancer.

Metasynthesis of European colorectal cancer screening studies

A narrowing down of uncertainty and adaptation of the model to specific European circumstances is currently being achieved by a meta-synthesis of data from colorectal cancer screening trials and observational studies performed in the European Union. The central hypothesis behind the meta-synthesis is that the outcomes from screening projects differ because of differences in local circumstances and differences in screening policy, while the natural history is identical across countries. Examples of local circumstances are demography, risk for colorectal cancer and quality of treatment. Aspects of screening policies are the applied screening tests, screening interval, compliance with screening, and the chosen method of evaluation, such as the method of data collection and the follow-up time. A model such as MISCAN-COLON can simulate specific local circumstances and characteristics. If the aforementioned central hypothesis is correct, comparing model predictions for a certain set of deep parameter values with the observed outcomes for a range of screening and surveillance projects (including FOBT and endoscopy as primary

screening tests), will enhance the precision of estimation of natural history assumptions. Validation of more aspects can be achieved than would be possible when only studying one screening project. If the central hypothesis is not correct, this may be demonstrated by overly large discrepancies between modeled and observed outcomes over the different projects using one set of deep parameter values. To explain such a result would need further investigation and meanwhile prohibit extrapolation of the outcomes of empirical studies to other circumstances. The meta-synthesis study concerns the following studies: the Funen adenoma surveillance trial, the Funen FOBT RCT, the Nottingham FOBT RCT, the Gothenburg FOBT RCT, the Burgundy FOBT screening program, the Florence FOBT program, the Telemark sigmoidoscopy screening trial, the Italian once-only flexible sigmoidoscopy (SCORE 1) trial, the Italian SCORE 2 trial on feasibility of several screening strategies, and the European multi-center trial on the addition of sigmoidoscopy to FOBT screening [Jørgensen 1993, Kewenter 1994, Bennett 1995, Castiglione 1996, Hardcastle 1996, Hoff 1996b, Kronborg 1996, Senore 1996, Berry 1997].

FOBT screening

Impact of systematic negative results

The impact of non-bleeding cancers on the effectiveness of FOBT screening was studied in Chapter 3. It was concluded that the impact of systematic false-negative test results is important if annual FOBT screening is the option under consideration. Thus, if the effect of annual FOBT screening is estimated from biennial FOBT screening programs, the possibility of systematic false-negative cancers should be given due attention. The absolute gain in colorectal cancer mortality reduction by changing the interval of FOBT screening from 2 to 1 years depends on the fraction of systematic negative test results, being approximately 8% if no systematic negative results occur and as low as 2% if all negative test results are systematic. We can compare these results with the observed colorectal cancer mortality reduction in the Minnesota Colon Cancer Control Study. This is the only study in which annual FOBT screening and biennial FOBT screening was performed. The absolute gain in mortality reduction by changing the screening interval from 2 to 1 years was (6.2-5.0)/7.5=16% (95% confidence interval –4% to 30%) [Mandel 1999]. According to our study, the extra absolute mortality reduction is approximately 8% if no systematic negative results occur and may be as low as 2% if all negative test results are systematic. The observed gain of 16% may be a chance finding, and 2% and 8% are both within the confidence interval of the observed gain. Furthermore, the model presented in Chapter 3 did not take into account the fact that some cancers will be detected by a positive FOBT result that is not caused by bleeding of the cancer. Some screenees will therefore have a FOBT test that is positive by chance. These screenees will undergo a diagnostic colonoscopy, at which colorectal cancer may well be detected. The Minnesota investigators found that 16-25% of the mortality reduction in the annually screened group was due to chance detection [Ederer 1997]. Because 16% is closest to 8% absolute gain in mortality reduction and because some cancers may be detected by chance, it is unlikely

that systematic negative test results play an important role in the Minnesota Colon Cancer Control Study.

Costs and savings of FOBT screening

In Chapter 4 of this thesis, it was shown that the costs of a sigmoidoscopy screening program in the United States with a 5 year screening interval might be compensated completely by the savings in treatment costs. The savings in treatment costs are caused by the prevention of colorectal cancer incidence due to the removal of adenomas. It is unlikely that the induced costs of FOBT screening will be able to be completely compensated by the savings in treatment costs, because FOBT screening aims to detect colorectal cancer instead of adenomas. However, one German study reported cost-savings by immunochemical FOBT screening [Sieg 1998]. In that study, 14 colorectal cancers were detected by screening, 10 of which were Dukes' A cancers that were removed by endoscopic polypectomy and did not require further treatment. In that study, the unit costs of cancer treatment was 14,149 DM, while the unit costs of the FOBT test was 10 DM and the cost of colonoscopy was 107 DM. In this small study, the savings exceeded the screening costs by approximately 2.3 times.

Possible adverse effect of FOBT screening on all-cause mortality

The authors of a meta-analysis of breast cancer screening trials [Gøtzsche 2000, Olsen 2001] noted that in some breast cancer screening trials the reduction in breast cancer mortality did not result in a reduction in all-cause mortality or cancer-related mortality. Recently, Black *et al.* [Black 2002] compared the difference in disease-specific and all-cause mortality in 12 randomized controlled screening trials, including 3 FOBT trials [Mandel 1993, Hardcastle 1996, Kronborg 1996]. Table 8.2 presents the colorectal cancer mortality and all-cause mortality in the trials studied by Black *et al.*, together with the updated results for the three trials. In all results, except the Funen 1996 results, the reduction in colorectal cancer mortality was higher than the all-cause mortality reduction. This inconsistency may be caused by "slippery-linkage bias" where screening induces mortality due to the screening test itself or to diagnostic and therapeutic interventions after a positive screening test. For example, colonoscopy could induce cardiovascular deaths. The Telemark sigmoidoscopy screening study also found an elevated all-cause mortality in the screen group [Thiis-Evensen 1999, Hoff 2001]. The Telemark investigators found no excess mortality in the screen group in the years of endoscopic activity and suggest that the increase in mortality in the screen group is caused by unfavorable changes in lifestyles among screening participants without polyps [Hoff 2001]. Hence all-cause mortality is lower than the reduction in colorectal cancer mortality in the most recent results of all three trials, and the Telemark study suggests that a negative endoscopy might adversely affect lifestyle. It is therefore recommended that lifestyle be registered in screen and control arms at the end of the study period of new and existing screening studies.

Table 8.2 Randomized trials of FOBT screening reporting colorectal cancer mortality and all-cause mortality. Adapted from [Black 2002].

Publication	Colorectal cancer mortality No. per 10,000 person-years			All-cause mortality No. per 10,000 person-years		
	Screen	Control	Screening benefit	Screen	Control	Screening benefit
Minnesota						
[Mandel 1993]	5.4	6.6	1.2 (0.1 to 2.4)	183.6	183.6	0.0 (-7.6 to 7.6)
[Mandel 1999]	5.6	7.5	1.9 (0.6 to 3.1)	217.5	218.4	1.0 (-6.3 to 8.2)
Nottingham						
[Hardcastle 1996]	6.0	7.0	1.0 (0.1 to 2.0)	211.1	209.9	-1.2 (-6.4 to 3.9)
[Scholefield 2002]	7.0	8.1	1.1 (0.3 to 1.9)	241.8	241.1	-0.7 (-5.4 to 4.0)
Funen						
[Kronborg 1996]	6.5	8.2	1.7 (0.3 to 3.2)	221.0	224.0	3.0 (-4.7 to 10.8)
[Jørgensen 2002]	8.3	9.7	1.4 (0.0 to 2.8)	247.8	248.1	0.2 (-7.1 to 7.6)

Endoscopic screening

Costs and savings of sigmoidoscopy screening in the United States

In Chapter 4 of this thesis, it was shown that the costs of a sigmoidoscopy screening program in the United States with a 5 year screening interval might be compensated completely by the savings in treatment costs. The costs of a screening strategy consist of the costs of the screening test itself, the costs of the diagnostic colonoscopy in individuals with lesions, and the costs of removal and pathology of polyps. In addition, the costs of treating complications due to screening or diagnostic procedures and the costs of surveillance of adenoma patients detected at screening should be considered. It was concluded that the induced costs of an efficient sigmoidoscopy screening program in the United States, including the costs of diagnosis and surveillance of adenoma patients, could be compensated completely by savings in cancer treatment.

In Chapter 5, the simulated results of the expert MISCAN-COLON model are compared with the observed results in the National Polyp Study. From this comparison it may be concluded that adenoma incidence is high and is accompanied by regression of adenomas. It would be interesting to investigate whether these assumptions affect the conclusion that the costs of 5-yearly sigmoidoscopy can be compensated by savings in treatment. Modifying the expert MISCAN-COLON model to include a high adenoma incidence together with adenoma regression leads to a result where the costs of screening are not completely compensated by the savings in treatment. According to this modified model, the induced costs of sigmoidoscopy screening are $258 per person in the total U.S. population in 1993. This is slightly higher than the estimated $208 stated in Chapter 4, and is caused by the high adenoma incidence rate in the modified model, resulting in numerous positive sigmoidoscopies and leading to additional costs for colonoscopic

diagnostics and surveillance. In the modified model, the savings in treatment are $173 per individual, or a net cost of $85 per individual member of the U.S. population.

Costs and savings of sigmoidoscopy screening in the Netherlands

Will the savings in treatment costs also compensate the costs of sigmoidoscopy screening in the Netherlands? To find out, the costs and savings of five-yearly sigmoidoscopy screening in the Netherlands were calculated by modifying the expert MISCAN-COLON model presented in Chapter 4 to simulate the colorectal cancer incidence and mortality and the age distribution in the Netherlands in 1997. The unit cost of sigmoidoscopy was assumed to be 100 EURO, the unit cost of colonoscopy 250 EURO. The treatment cost of colorectal cancer was assumed to be 8000 EURO and the cost of palliative care 14,000 EURO. These costs were based on hospital data sources and interviews. The costs of palliative care were estimated from cost studies in the United States [Kwaliteitsinstituut voor de gezondheidszorg CBO 2002]. Table 8.3 shows that in the Netherlands, savings in cancer treatment are expected to compensate only 39% of the induced costs of five-yearly sigmoidoscopy screening. According to these calculations, the net costs of a five-yearly sigmoidoscopy screening program in the Netherlands will amount to approximately 110 million Euro per year .

The difference in results is caused by the high ratio between the unit cost of a sigmoidoscopy and the cost of cancer treatment relative to the cost assumptions in Chapter 4 for the United States. To arrive at an approximation of the average costs of treatment of a newly diagnosed colorectal cancer patient, the costs of initial treatment were taken, plus 50% of the costs of palliative care, as approximately 50% of the colorectal cancer patients die from the disease. The ratio between the approximated cost of cancer treatment and the cost of a sigmoidoscopy is then 33,000/100=330 in the model described in Chapter 4 and 150 in the model for the Netherlands. The assumed unit costs of primary treatment was 70% lower than in the United States, while the unit costs of

Table 8.3 Three percent discounted induced costs and savings (EURO) of every 5-year sigmoidoscopy screening in age group 50-75 years from 1997 through 2027 per person in the Netherlands. Results of the expert MISCAN-COLON model. (See also Table 4.2)

Costs of screening	122	
Costs of colonoscopic diagnostics during screening, including polypectomy and complications	32	
Costs of surveillance, including polypectomy and complications	57 +	
Total screening induced costs		210
Savings of primary treatment	40	
Savings of control visits	0	
Savings of terminal treatment	41 +	
Total screening induced savings		81
Net screening costs		129

sigmoidoscopy, colonoscopy and palliative care in the Netherlands were assumed to be comparable with unit costs in the United States. It is unclear why the unit costs of primary treatment in the Netherlands differ so very strongly from the costs in the United States; a possible explanation could be the longer surgery and more advanced techniques applied in the United States than in the Netherlands. It may therefore be concluded that, while the savings in treatment completely compensate the costs of screening in the United States, it is unlikely that these will completely compensate the costs of sigmoidoscopy screening in the Netherlands.

Costs and savings of sigmoidoscopy screening according to other cost analyses

Whether savings compensate costs is largely dependent on the ratio between the unit cost of a screening test and the cost of cancer treatment. In the past few years, several cost studies of colorectal cancer screening have been published. Table 8.4 shows the unit cost of sigmoidoscopy and colonoscopy, the unit cost of cancer treatment, and the resulting costs per lifeyear gained in the studies that evaluate endoscopic screening. The discount factor is also shown. Two studies were not included because they concentrated on FOBT screening and did not calculate the cost-effectiveness of endoscopic screening [Eddy 1990, Neilson 1995]. A systematic comparison of assumptions in these models has been published recently [Pignone 2002]. Except for our study, which used the MISCAN-COLON model [Loeve 2000] and the study of Ness *et al.* [Ness 2000], the induced savings of endoscopic screening were found not to compensate the costs of screening. This is mainly because the ratio between the unit costs of colonoscopy and the costs of treatment is smaller than that assumed in Chapter 4 of our study [Lieberman 1991a, Lieberman 1995, Frazier 2000].

Furthermore, the strength of time preference (discounting) is important, because of the long period between the time at which an adenoma is detected by screening and the point at which the subsequent cancer would have been diagnosed and treated had no screening been performed. Hence the savings in treatment occur many years after the costs of screening. If the discount factor is high, the savings calculated back to the reference year for discounting are small. In that case, later savings are less likely to compensate the costs of screening. Two models do not simulate cost-savings because a larger discount factor is used than the 3% used in our study [Wagner 1996, Khandker 2000]. Wagner, who used the OTA model [Wagner 1996], discounted the costs and savings of colorectal cancer screening at 5% instead of the 3% applied in our study.

Screening-induced savings are mainly due to the prevention of cancer and therefore represent savings on cancer treatment. Assumptions on the effect of screening, such as assumptions on the natural history of colorectal cancer and the test sensitivity of sigmoidoscopy and colonoscopy, also influence the net costs. In the OTA model, for example, adenomas are assumed to develop into cancer after an average of 10 years, while the expert MISCAN-COLON model assumes an average of 16.4 years [Wagner 1996]. Furthermore, in the OTA model it is assumed that 70% of the cancers originate from adenomas, while in the expert MISCAN-COLON model used in Chapter 4 it is assumed that all cancers originate from adenomas. The MISCAN-COLON assumption that 100%

Table 8.4 Ratio of costs of sigmoidoscopy (sigmo), colonoscopy (cscpy) and treatment costs in the baseline model of several cost-effectiveness analyses of endoscopic screening in the United States. Cost-effectiveness ratio is calculated as costs per lifeyear gained compared with no screening, unless stated otherwise. SR=Ratio treatment costs/ costs sigmoidoscopy; CR=Ratio treatment costs/ costs colonoscopy; CPR=Ratio treatment costs/ costs colonoscopy with polypectomy; CER=cost effectiveness ratio.

Author	Discount rate	Costs sigmo	Costs cscpy	Costs cscpy including polypectomy	Costs treatment	SR	CR	CPR	CER baseline model
[Ness 2000]	3%	-	$303	$530	$26,895***	-	89	51	once-only cscpy: from $215 for females age 45-49 to -$2422 for males age 60-64
[Loeve 2000]	3%	$100	$300	$400	$33,000*, **	330	110	83	5 yr. sigmo: -$179
[Wagner 1996]	5%	$80	$285	$434	$40,000****	500	140	92	5 yr. sigmo: $11,947 10 yr. sigmo: $20,122 10 yr. cscpy: $22,171
[Frazier 2000]	3%	$279	$1012	$1519	$41,400***	148	41	27	5 yr. sigmo: $12,571 10 yr. cscpy: $20,418
[Khandker 2000]: individuals aged <65 yr.	4.8%	$176	$670	$981	$54,768***	311	82	56	5 yr. sigmo: $12,636 10 yr. cscpy: $17,696
individuals aged>65 yr.	4.8%	$94	$438	$702	$54,768***	583	125	78	see above
[Sonnenberg 2000]	3%	$401	$696	$1004	$45,228	113	65	45	5 yr. sigmo: $74,032 10 yr. cscpy: $28,143
[Lieberman 1991a]	0%	$150	$1100	$1700	$22,500****	150	20	13	Per death prevented: once-only cscpy: $347,214
[Lieberman 1995]	0%	$150	$1000	$1500	$25,000	167	25	17	Per death prevented: 5-yearly sigmo: $258,000 once-only cscpy: $274,000

* The costs of control visits are neglected

** Assuming that 50% of CRC patient receive palliative care

*** Assuming that 33% of the cancers are localized, 33% are regional and 33% are distant

**** Assuming that 50% of the cancers are early and 50% are late

of the cancers originate from adenomas was based on expert opinion. The OTA model assumed 70% because even though most experts agree that the great majority of the cancers evolve in accordance with the polyp-cancer sequence, Morson and colleagues found that only 57% of very early cancers were unequivocally located in a benign adenoma [Morson 1974]. The assumptions in the OTA model will result in fewer prevented cancers than those in the expert MISCAN-COLON model, which means that the savings in cancer treatment in the OTA model will automatically be lower than in the expert MISCAN-COLON model.

Surveillance of adenoma patients

Colorectal cancer incidence in adenoma patients

Another of the research questions that this thesis proposed to address concerns the estimation of colorectal cancer incidence after adenoma removal throughout the years immediately following the polypectomy. Adenomas are considered precursors of colorectal cancer and are therefore removed, after which patients should be regularly surveilled. Surveillance examinations in adenoma patients affect the colorectal cancer incidence. On the one hand, cancer incidence decreases because of the removal of adenomas at surveillance examinations, while on the other hand, the incidence of colorectal cancer rises as a result of early detection of asymptomatic cancers at surveillance colonoscopies. Several studies have shown that patients in whom adenomas are not removed are at increased risk for colorectal cancer. Table 8.5 shows the relative colorectal cancer risk in adenoma patients who did not undergo an initial colonoscopy and polypectomy. A low relative risk estimate of 1.2 was found in the Atkin study in which adenoma patients underwent sigmoidoscopic polypectomy [Atkin 1992] and in the Spencer study of patients with small (≤1cm) polyps [Spencer 1984]. A high relative risk estimate of 4.0 was found in the Otchy study at a site distant from the index polyp in patients whose large polyps were followed with radiographic examinations [Otchy 1996]. A previous publication of the same research group reported on the colorectal cancer incidence at the site of the index polyp [Stryker 1987]. Unfortunately, however, in that publication the colorectal cancer incidence was not compared with the general population. In that study, 226 patients with colorectal polyps ≥1cm were followed with annual radiographic examination for a mean of 5.7 years. During the follow-up period, 21 colorectal cancers were discovered at the site of the index polyp and 11 at a site distant from the index polyp. If these results are combined, the colorectal cancer incidence was as much as 2,500 per 100,000 person years, while the colorectal cancer incidence in the general population increases with age and is in any case below 700 per 100,000 person years in the oldest age groups. However, it is possible that some of these patients had already developed cancer in the index polyp at the time of the initial examination. The conclusion of this overview is that it is plausible that the risk for colorectal cancer in adenoma patients is several times the colorectal cancer risk in the general population.

Table 8.5 Relative colorectal cancer risk compared to the general population for adenoma patients who did not undergo an initial colonoscopy.

Study	No. patients	Mean follow-up period (yr.)	Relative risk	Remark
[Prager 1974]	283	15	3.0	Colon cancer incidence out of reach of the rigid sigmoidoscope in patients who underwent sigmoidoscopic polypectomy and surveillance sigmoidoscopy.
[Spencer 1984]	751	13.5	1.2	Patients whose small (1cm or less) colorectal polyps were treated by fulguration (98%) or observation alone (2%) in the period 1950-69
[Lotfi 1986]	323	13.4	2.7	Patients with colorectal polyps of whom 97% had their index polyp excised or fulgurated in the period 1950-69
[Atkin 1992]	1618	13.9	2.1	Incidence of colon cancer in patients who had adenomas removed via rigid sigmoidoscopy and who were not regularly surveilled by colonoscopy
[Atkin 1992]	1618	13.9	1.2	Incidence of rectum cancer in patients who had adenomas removed via rigid sigmoidoscopy and who were not regularly surveilled by colonoscopy
[Otchy 1996]	226	9.4	4.0	Incidence of cancer at a site distant from the index polyp in patients followed with radiographic examination

In order to investigate the colorectal cancer risk after polypectomy in actual clinical practice, we reviewed all studies on relative colorectal cancer risk after polypectomy. Furthermore, we studied the incidence of colorectal cancer in 553 consecutive adenoma patients in the endoscopy department of the Slotervaart Hospital, Amsterdam, and in all 78,473 adenoma patients in the period 1 October 1988-1 October 1998 in the Netherlands. The review in Chapter 6, including the results of the Slotervaart study, showed that the colorectal cancer risk in the first years after colonoscopic polypectomy in selected adenoma patients who undergo high-quality initial colonoscopy and polypectomy and regular surveillance does not exceed the colorectal cancer risk in the general population. It is suggested that the risk for patients with non-

sessile adenomas is lower than in the general population. Chapter 7 reports the cancer incidence in adenoma patients in the PALGA registry, a nation-wide Dutch pathology registry. The study shows that, with the current polypectomy and surveillance practice, adenoma patients have a significantly higher risk for colorectal cancer than the general population, as evidenced by the incidence ratio of 1.5 (1.4-1.6) on excluding the year immediately following initial adenoma removal. The standardized incidence ratio declined from 2.8 (2.5-3.1) in the second year to 0.9 (0.6-1.2) in year 9-11 after adenoma removal was first performed. It is hypothesized that cancers missed during the diagnostic process cause the high cancer incidence in the first years after polypectomy, even until the fifth year after adenoma removal. This is supported by the fact that the results are consistent with a colonoscopic sensitivity for cancer of approximately 90%. Further evidence for the "missed cancers" concept may lead to modified clinical guidelines for diagnostic work-up of suspected colorectal cancer patients. (Chapter 7).

Costs and effects of surveillance of adenoma patients in the Netherlands

The surveillance strategy of adenoma patients is an essential part of a screening strategy, because screening will detect adenoma patients. This is straightforward for colonoscopy and sigmoidoscopy screening, but FOBT screening will also detect extra adenoma patients. In 1988, the first surveillance guidelines for adenoma patients in the Netherlands were published [Snel 1988]. Since then, the National Polyp Study has reported that surveillance colonoscopy at 1 year after initial polypectomy is not needed and that the first surveillance colonoscopy after initial colonoscopy can be performed after 3 years [Winawer 1993b].

In revising the 1988 Dutch guidelines, the effects and costs of several surveillance strategies after polypectomy of colorectal adenomas were calculated with the MISCAN-COLON model [Kwaliteitsinstituut voor de gezondheidszorg CBO 2002]. The expert MISCAN-COLON model was adjusted to reproduce available relevant data, such as colorectal cancer incidence in the Netherlands and adenoma prevalence in autopsy studies. An alternative model assumed that the sensitivity of colonoscopy for adenomas <10mm is only 60% instead of the 80-85% assumed in the expert MISCAN-COLON model. The alternative model was more consistent with the findings observed in the Palga registry, which are reported in Chapter 7, than the MISCAN-COLON expert model. Unit cost estimates were based on literature and data from the Academic Hospital Rotterdam. The following surveillance strategies were considered: no surveillance, once-only surveillance at 10, 6, or 3 years after initial polypectomy, surveillance every 3 years, surveillance every 6 years, and the 1988 guidelines.

Costs and lifeyears gained as a result of a surveillance strategy compared with a situation without surveillance were discounted at 3% per year. The reference year for discounting was the year in which the initial polypectomy was performed. The cost-effectiveness ratio of a surveillance strategy was calculated by dividing the costs of the surveillance strategy by the lifeyears gained due to surveillance. The incremental cost-effectiveness of a surveillance strategy compared with a less intensive strategy is the ratio between the extra costs of the intensive strategy and the extra lifeyears gained by the intensive strategy. A surveillance strategy was considered to be efficient if there were no

alternative strategy resulting in more lifeyears gained with equal or less costs. A cost-effectiveness ratio of less than 14,000 EURO per lifeyear gained compared with no surveillance was considered to be favorable. This is comparable with the cost-effectiveness ratio of cervical cancer screening [van Ballegooijen 1993].

In the expert MISCAN-COLON model, the costs per lifeyear gained compared to no surveillance were less than 3000 EURO for all considered surveillance strategies. The following efficient strategies (i.e., strategies unable to be improved upon in both costs and effects by other strategies) were identified for patients with one adenoma at initial colonoscopy: once-only surveillance after 10 years, surveillance every 6 years, the Dutch guidelines of 1988, and surveillance every 3 years. The costs per lifeyear gained increased with the intensity of the surveillance strategy. Efficient strategies for patients with initially 2 adenomas and patients with 3 or more adenomas were: surveillance every 6 years, surveillance every 3 years and the Dutch recommendations of 1988. Savings in cancer treatment were larger than the costs of surveillance for patients with 3 or more adenomas receiving surveillance every 6 years. In the MISCAN-COLON model with less (60%) sensitivity for adenomas smaller than 10mm than in the expert MISCAN-COLON model, the costs per lifeyear gained compared with no surveillance were less favorable for all strategies, but still favorable compared with cervical cancer screening. For example, surveillance every 3 years in patients with 3 or more adenomas was net cost-saving in the expert MISCAN-COLON model, while the costs per lifeyear gained were 100 EURO according to the MISCAN-COLON model with the low sensitivity of colonoscopy.

In conclusion, surveillance every 6 years, surveillance every 3 years and the 1988 Dutch guidelines were efficient strategies. The results of the MISCAN-COLON simulations combined with the results of the National Polyp Study indicate that it is reasonable to lengthen the follow-up interval to 6 years for patients with 1 or 2 adenomas and to use a 3 year follow-up interval for patients with 3 or more adenomas. The Dutch guidelines on surveillance of adenoma patients were consequently revised [Nagengast 2001, Kwaliteitsinstituut voor de gezondheidszorg CBO 2002]. It is now recommended that patients with one or two adenomas be offered a surveillance colonoscopy 6 years after the initial polypectomy. If three or more adenomas are found at initial colonoscopy, patients should receive a surveillance colonoscopy 3 years after the initial polypectomy. If fewer than three adenomas are detected at surveillance colonoscopy, the next surveillance colonoscopy should be performed 6 years later. If three or more adenomas are detected at surveillance colonoscopy, the next surveillance colonoscopy should be performed 3 years later. Surveillance can stop at age 65 in patients with cumulative 1 adenoma, and at age 75 in patients with cumulative 2 adenomas. Surveillance in patients with cumulative 3 adenomas or more should continue as long as the patient’s health permits. If no adenomas are found in 3 consecutive surveillance colonoscopies, surveillance can stop.

Low risk adenoma patients

If screening is introduced in the Netherlands, the surveillance strategy of adenoma patients should not be too intensive. An intensive surveillance strategy requires a large colonoscopy capacity and induces unnecessary complication risks to adenoma patients, while the extra incidence reduction is not expected to balance these costs and risks. A

large group of adenoma patients in whom all adenomas are removed is probably at low risk for colorectal cancer, even lower than the general population due to the removal of the adenomas. These patients do not require colonoscopic surveillance and can be screened in the same way as other individuals. This will decrease the demand for surveillance colonoscopy. The main characteristics that are used to distinguish low-risk from other adenoma patients are the age and sex of the patient, and histology, dysplasia, size, and multiplicity of adenomas. The datasets currently available are not suitable for concluding which risk group of adenoma patients is at low or average risk for colorectal cancer. The study populations of the National Polyp Study and the Funen Adenoma Surveillance Study are too small. The number of colorectal cancer patients diagnosed during the study period was 5 and 11 respectively. In the National Polyp Study, advanced adenomas were more frequently detected in patients with three or more adenomas at baseline colonoscopy, in patients with a positive family history of colorectal cancer, and in patients age 60 years or older. The dataset from the Slotervaart Hospital, Amsterdam, The Netherlands, contains no information on the multiplicity and histology of adenomas and is also a small dataset. The Palga dataset (Chapter 7) is large enough, but contains no data on the performed colon examination (sigmoidoscopy or colonoscopy), or on the multiplicity and size of the adenomas and only limited data on histology of the adenomas. A nation-wide or regional adenoma and colorectal cancer database would facilitate the study of the risk of colorectal cancer in adenoma patients. The age and sex of each adenoma patient should be registered. Furthermore, the date of each colon examination should be registered together with the reason, the method of examination, and the reach, the histology, size, multiplicity and grade of dysplasia of the detected adenomas. The registry should include negative colon examinations. The database should be linked regularly with the cancer registry of the Palga registry to register colorectal cancer diagnosis.

New colorectal cancer screening tests

DNA markers in feces

Tests to detect DNA mutations in feces appear to be promising screening tools. Most tests focus on detecting K-*ras* mutations or mutations in the adenomatous polyposis coli (*APC*) gene [Ahlquist 2000a, Ahlquist 2000b, Traverso 2002]. Some researchers have suggested using the amount of human DNA in feces as a screening test [Loktionov 1998]. Ahlquist *et al.* tested multiple DNA markers in the feces of 22 patients with colorectal cancer, 11 patients with adenomas ≥ 1cm, and 28 patients with normal colons [Ahlquist 2000b]. They found a 91% sensitivity for cancer, 82% for adenomas ≥ 1cm and a specificity of 93%. Traverso *et al*. screened for *APC* mutations in the feces of 28 patients with colorectal cancer, 18 patients with adenomas ≥ 1cm and 28 control patients without neoplastic disease [Traverso 2002]. They found a 61% sensitivity for cancer, 50% for adenomas ≥ 1cm and a specificity of 100%. The sensitivity of these tests for adenomas <1cm has not been studied. The advantage of testing for DNA markers in feces compared with guaiac Hemoccult FOBT testing is that no diet is required. However, the tests are currently too

labor-intensive for screening purposes. Furthermore, in these studies, with the exception of the Ahlquist study [Ahlquist 2000b], the feces had to be stored at -80°C immediately after collection, which means that collection of the stools should be performed at the hospital. It will take several years and probably longer before this kind of test can be used for screening.

Virtual colonoscopy

Next to FOBT, sigmoidoscopy and colonoscopy, virtual colonoscopy also offers possibilities for screening. During a virtual colonoscopy, computed tomography (CT) or magnetic resonance imaging (MRI) visualizes the colorectal tract. CT is less costly than MRI, but involves ionizing radiation that can cause cancer, unlike MRI [American Society for Gastrointestinal Endoscopy 1998, Farrell 1999]. The cleansing preparation for the test is comparable with the preparation for conventional colonoscopy. The advantage of virtual colonoscopy compared with conventional colonoscopy is that no sedation is required, which reduces the risk of complications. A drawback of virtual colonoscopy compared with conventional colonoscopy is the fact that a conventional colonoscopy is still needed if lesions are detected at virtual colonoscopy. The sensitivity for cancer and large polyps appears to be comparable to that of conventional colonoscopy. However, the sensitivity for small adenomas is lower than the sensitivity of conventional colonoscopy [Fenlon 1999, Lameris 2000, Pappalardo 2000, Pescatore 2000]. Furthermore, the specificity of virtual colonoscopy is low. Yee *et al.* found that, in 118 individuals with a normal conventional colonoscopy, up to 33 had a positive virtual CT colonoscopy (specificity 72%) [Yee 2001]. Lastly, it currently takes too long to process the images derived during virtual colonoscopy (30-60 minutes) for this to be applied for screening purposes. By comparison, a colonoscopy, performed by an experienced endoscopist [Winawer 1997] takes only 15-20 minutes [Bond 1999, Pappalardo 2000]. This drawback may be solved in the coming years by computerized polyp detection.

Immunochemical FOBT tests

The guaiac Hemoccult FOBT test was used in all trials that reported a significant reduction in colorectal cancer mortality by FOBT screening. Meanwhile, immunochemical tests have been developed, which seem to have a better sensitivity for cancer than the unrehydrated Hemoccult test, while the specificity is comparable [Castiglione 1996, Castiglione 1997, Rozen 1997, Zappa 2001]. The effect of these immunochemical tests on colorectal cancer mortality is unknown, as these tests have not been used in randomized trials so far. However, immunochemical tests seem promising for use as screening tests, because more cancers can be detected than by guaiac tests, which could lead to a larger reduction in mortality. In an Italian population-based screening program, colorectal cancer incidence after an immunochemical FOBT test was reduced by 82%, while the incidence after a guaiac FOBT test was reduced by 50% [Zappa 2001]. Another advantage of the immunochemical tests is that no dietary restrictions apply [Rozen 1997]. Furthermore, some of the immunochemical tests, such as the latex agglutination test, are quantitative tests, allowing the cut-off point to be chosen [Castiglione 2000]. The advantage of the latex agglutination test over the RPHA test is that the former can be developed by a

completely automated procedure [Castiglione 2000]. Immunochemical FOBT tests are currently being used for screening in Italy [Castiglione 2000] and Japan [Nakama 1996].

Criteria of Wilson and Jungner applied to colorectal cancer screening in the Netherlands

In this section, we apply the criteria of Wilson and Jungner to FOBT and endoscopic screening in the Netherlands.

1. The disease should be an important health problem

As stated in the Introduction to this thesis, colorectal cancer is one of the most frequent cancers in Western countries and the Netherlands. The cumulative risk of dying from colorectal cancer before the age of 75 is 1.9% for men and 1.2% for women [Visser 2001]. Total elimination of colorectal cancer would add 4.5 months to the life expectancy of a 50-years old person. Thus, colorectal cancer is a major health problem.

2. There should be an accepted treatment for patients with recognized disease

FOBT mainly aims to detect early invasive colorectal cancer. As stated in the Introduction to this thesis, patients with colorectal cancer usually undergo surgery to remove the cancer and part of or the entire colon. Some patients subsequently receive chemotherapy. Patients with adenomas have their adenomas removed during an endoscopic procedure. It is generally assumed that removal of adenomas reduces subsequent colorectal cancer incidence and mortality. In conclusion, there is an accepted treatment for patients with adenomas and colorectal cancer.

3. Facilities for diagnosis and treatment should be available

Besides facilities for diagnosis and treatment, facilities for screening itself should also be available. Screenees perform the FOBT test at home, but the test is processed in a laboratory. The present laboratory capacity for FOBT screening is probably insufficient. Nor should general practitioners be expected to play a more active role in FOBT screening, such as bearing the responsibility for sending and processing the FOBT kits, as they are already overburdened.

Regardless of whether FOBT, sigmoidoscopy or colonoscopy screening is introduced, the demand for endoscopy will increase. The capacity to perform endoscopy in the Netherlands is presently insufficient to meet this demand. In the future, more gastroenterologists can be trained. Since colonoscopy usually requires sedation and complications may occur during colonoscopy, it is currently not clear whether trained nurses can perform colonoscopy safely. Sigmoidoscopy screening is efficiently performed in the CoCap program in the United States where more than 300 general physicians and non-physicians have been trained to perform screening sigmoidoscopy [Palitz 1997]. The possibility of training nurse sigmoidoscopists can be studied in a pilot project.

Most cancers detected by FOBT would also be detected without screening, but at a later moment. Thus, the capacity for cancer treatment does not need to be enlarged. However, if population screening is suddenly introduced in the Netherlands, many (early)

preclinical cancers will be detected in the population within a short period. The capacity to treat these patients should be sufficiently large. Later on, FOBT screening will mainly detect newly developed cancers and the present capacity should be sufficient. The demand for adjuvant therapy will probably decrease, as many cancers will be detected at an earlier stage.

Sigmoidoscopy and colonoscopy are mainly intended to detect adenomas that, without screening, would have gone undetected in the absence of any symptoms. In some cases, large adenomas are removed during surgery. It is not clear whether the introduction of an endoscopic screening program will require an increase in adenoma surgery capacity. On the one hand, adenomas requiring surgical treatment will be detected in some screenees that, without screening, would have remained undetected. On the other hand, adenomas that would have required surgical removal as soon as the initial symptoms appeared will, following the introduction of a screening program, be detected earlier and not require surgical treatment at all. The demand for cancer treatment and adjuvant therapy is likely to decrease a few years after the introduction of sigmoidoscopy or colonoscopy screening, as these tests aim to prevent cancer and thus prevent cancer treatment.

In conclusion, the capacity to process FOBT tests is presently insufficient for population-based FOBT screening. Furthermore, the endoscopic capacity is insufficient to meet the demand induced by FOBT, sigmoidoscopy or colonoscopy screening. Screening will also increase the demand for colorectal cancer treatment in the first years of the screening program due to the early detection of preclinical cancer. If sigmoidoscopy or colonoscopy screening is introduced, the demand for cancer treatment and adjuvant therapy will decrease after a few years.

4. There should be a recognizable latent or early symptomatic stage

In the section “Natural history” in the introduction, the adenoma-carcinoma sequence is explained. Both adenomas and preclinical colorectal cancer are precursors of symptomatic colorectal cancer. However, not all adenomas will become malignant and our study of the National Polyp Study suggests that adenomas may regress to normal tissue (see Chapter 5).

5. There should be a suitable test or examination

FOBT is a simple test that can be performed at home. FOBT is not acceptable as a diagnostic test, because a positive FOBT test can easily be caused by a mundane problem like hemorrhoids, yielding a false-positive test result. The test is suitable for screening purposes as it can detect a large proportion of the preclinical cancers. Wilson and Jungner state that a fairly high false-positive rate is acceptable in screening but the false-negative rate should be very low, since missed cases may lead to individual disasters. However, in practice, a high false-positive rate is undesirable. For example, the rehydrated FOBT test has a specificity of 90%, which means that 10% of the screenees without adenomas or cancer will have a positive test. These screenees must all undergo colonoscopy and will be concerned about the chance of having colorectal cancer. As FOBT aims to detect cancer early, tests will be performed every few years and each time, 10% of the screenees will

have a positive test. To avoid these negative effects, an FOBT test with a higher specificity and a slightly lower sensitivity would be more suitable than rehydrated FOBT. Immunochemical FOBT tests are suitable tests, because of their high specificity and the fact that no dietary restrictions apply; these tests react with human hemoglobin only.

Sigmoidoscopy and colonoscopy are less easy to perform than FOBT. Both require cleaning of the colorectal tract before the test and the tests are unpleasant. The burden can be reduced by an easy preparation for the examinations, preferably in the endoscopy unit immediately before the examination. In the NORCCAP study, a small enema was administered at the screening center [Grotmol 2001]. In the UK Flexible Sigmoidoscopy Screening Trial, participants unwilling to use an enema at home were given the option of having the enema in the unit [UK Flexible Sigmoidoscopy Screening Trial Investigators 2002]. Colonoscopy requires sedation and the screenee will be unable to work the day of the colonoscopy. The possibility of performing colonoscopy without sedation is currently being studied in the NORCCAP study [Hoff 2000, Bretthauer 2002]. The advantage of sigmoidoscopy and colonoscopy is that they can detect cancer and adenomas, precursors of cancer. Most adenomas within reach of sigmoidoscopy or colonoscopy will be detected, which means that the proportion of screenees with false-negative results will be small. A drawback of sigmoidoscopy and colonoscopy is the (small) risk of complications, i.e., bleeding and perforation of the bowel. In short, it may be concluded that FOBT tests are more suitable for screening than are sigmoidoscopy and colonoscopy.

6. The test should be acceptable to the population

The compliance rate with screening is an indication of whether or not a screening test is acceptable for the population. In the Minnesota FOBT trial, where the participants were volunteers, 75-78% of all offered screening tests were accepted [Mandel 1993]. Compliance in the other three FOBT trials was lower, ranging from 53% compliance with the first screening in the Nottingham trial to 67% compliance with the first screening in the Funen trial [Kewenter 1994, Hardcastle 1996, Kronborg 1996]. The participants in these trials were drawn from the general population. Compliance in randomized controlled trials is usually higher than in a screening program. However, the evidence for the effectiveness of screening also influences the compliance rate. For example, in the Dutch pilot breast cancer screening projects in Utrecht and Nijmegen attendance was lower than in the current breast cancer screening program in the Netherlands.

Reported compliance with sigmoidoscopy screening varies from more than 80% in the Telemark study [Thiis-Evensen 1999] to less than 30% in a feasibility study in Italy [Senore 1996]. The once-only sigmoidoscopy trial in the United Kingdom reported 71% compliance in individuals who reported an interest in screening [UK Flexible Sigmoidoscopy Screening Trial Investigators 2002]. The compliance with sigmoidoscopy screening in the Netherlands has been studied in patients aged 50-60 years who visited an internal medicine outpatient clinic [Kremers 2000]. Two hundred patients were asked to be included in the study. Only 90 patients (45%) agreed to participate in sigmoidoscopy screening and to complete a questionnaire, 60 patients agreed to complete a questionnaire and 50 did not participate in the study at all. It may therefore be concluded that the

compliance rate with colorectal cancer screening is unclear and will be influenced by the evidence for the effectiveness of screening.

7. The natural history of the disease, including development from latent to declared disease should be adequately understood

FOBT screening focuses on detecting preclinical cancer. Three randomized controlled trials showed that early detection of preclinical cancer reduces colorectal cancer mortality. Thus, for FOBT screening, the natural history of the disease is adequately understood. Endoscopic screening focuses on detection and removal of adenomas. As stated before, most colorectal cancers are believed to develop from adenomas. This is a slow process [Muto 1975, Morson 1984]. It is generally thought that other lesions, such as hyperplastic polyps are not precursors of cancer and that these patients do not need surveillance [Winawer 1997], although a recent publication indicates that some hyperplastic polyps are a risk for colorectal cancer [Hamilton 2001, Hawkins 2001]. The effect of endoscopic screening on colorectal mortality has not been studied yet in large randomized trials. The conclusion is therefore warranted that the natural history is understood sufficiently well to introduce FOBT screening, but not sigmoidoscopy and colonoscopy screening.

8. There should be an agreed policy on whom to treat as patients

If a screening program is introduced, guidelines should be available stating what the follow-up strategy is for screenees with a positive test and what the follow-up strategy is for adenoma patients and colorectal cancer patients. Colorectal cancer patients should definitely be treated by an operation.

All guidelines state that adenomas should be removed immediately by polypectomy and that detection of an adenoma at sigmoidoscopy should be followed by colonoscopy [Winawer 1997]. However, in the UK Flexible Sigmoidoscopy Screening Trial, polyps smaller than 3mm in diameter in the distal 5cm of the rectum are not removed at the discretion of the endoscopist if they are judged to be hyperplastic [UK Flexible Sigmoidoscopy Screening Trial Investigators 2002]. In the CoCaP sigmoidoscopy program, if a single small polyp (<6mm) is identified at sigmoidoscopy, the polyp is removed but diagnostic colonoscopy is not indicated. If a single polyp of 6-9mm in size is detected at sigmoidoscopy, the physician decides whether or not to perform a colonoscopy. Diagnostic colonoscopy is performed in the CoCaP program after the detection of a single large polyp or multiple polyps at sigmoidoscopy [Palitz 1997].

Recent guidelines for surveillance of adenoma patients after polypectomy in the Netherlands recommend that patients with adenomas be examined by colonoscopy. Patients with 1 or 2 adenomas at the initial colonoscopy are surveilled after 6 years, patients with more than 2 adenomas are surveilled after 3 years [Nagengast 2001]. These guidelines are based on patients with adenomas that were mainly diagnosed due to symptoms. These guidelines should probably be revised if the majority of adenoma patients are diagnosed due to screening, because adenoma patients detected by screening have other characteristics than patients with adenomas detected due to symptoms.

9. The cost of case-finding, including diagnosis and treatment of patients diagnosed, should be economically balanced in relation to possible expenditure on medical care as a whole

This principle is related to cost-effectiveness analysis. Several costs- and cost-effectiveness studies on colorectal cancer screening have been published for other countries [Frazier 2000, Khandker 2000, Sonnenberg 2000] [Lieberman 1995, Wagner 1996, Gyrd-Hansen 1998, Whynes 1998]. The studies concluded that the cost-effectiveness of FOBT and endoscopic screening is acceptable and compares favorably with the cost-effectiveness of other cancer screening strategies, such as breast cancer screening and cervical cancer screening. It is unlikely that the cost-effectiveness of FOBT screening in the Netherlands will differ from the cost-effectiveness in other countries. The cost-effectiveness of sigmoidoscopy and colonoscopy study can be calculated with more certainty when the results of the UK Sigmoidoscopy Screening Trial are available [UK Flexible Sigmoidoscopy Screening Trial Investigators 2002].

10. Case finding should be a continuing process and not a "once and for all" project

Screening should not be a single occasion examination that occurs only once in history. A continuous screening program should be established, and screening should regularly be offered to the population. This means that a screening organization should be set up in the same way as the organization of breast and cervical cancer screening. A once-only colonoscopy screening program also satisfies this principle, as individuals of the appropriate age will be invited for screening each year.

Colorectal cancer screening in the Netherlands

Why should screening for colorectal cancer be introduced in the Netherlands

The efficacy of FOBT screening in reducing colorectal cancer mortality has been proven in three randomized controlled trials, see Table 8.2. Furthermore, several costs- and cost-effectiveness studies have been published for other countries. The studies concluded that the cost-effectiveness of FOBT screening is acceptable and compares favorably with the cost-effectiveness of other cancer screening strategies, such as breast cancer screening and cervical cancer screening [Gyrd-Hansen 1998, Whynes 1998]. The cost-effectiveness of FOBT screening in the Netherlands is unlikely to differ much from the cost-effectiveness in other countries. In conclusion, there is sufficient evidence for the effectiveness and cost-effectiveness of FOBT screening to introduce FOBT screening for colorectal cancer in the Netherlands. However, it is not clear whether FOBT screening is feasible in terms of compliance and capacity and which FOBT screening strategy is to be preferred. Some Dutch clinicians maintain reservations about FOBT screening and prefer endoscopic screening.

The efficacy of sigmoidoscopy in reducing colorectal cancer mortality has not been proven in large randomized trials. Until the results of the UK sigmoidoscopy study

become available [UK Flexible Sigmoidoscopy Screening Trial Investigators 2002], there is insufficient evidence to introduce sigmoidoscopy screening in the Netherlands.

Colorectal cancer screening guidelines have recently been published in other countries [Canadian Task Force on Preventive Health Care 2001, U.S. Preventive Service Task Force 2002]. It is important to develop guidelines for colorectal cancer screening in the Netherlands. If screening is not offered to individuals with a "normal" risk for colorectal cancer, "spontaneous screening" might become widespread. The demand for spontaneous screening has been observed before in and outside the Netherlands, especially for cervical cancer and prostate cancer screening [Bjorge 1993, Sigurdsson 1995, Bos 2002]. Spontaneous screening is less effective and efficient than systematic screening and can cause adverse health effects. This is due to the fact that fewer individuals are reached and that the screening is not performed at the optimum age and with the optimum screening interval. Furthermore, in a situation of spontaneous screening, it is difficult to monitor the favorable and unfavorable effects of screening, which makes it difficult to optimize screening and to monitor the quality of screening.

Screening studies in the Netherlands

In 2001, the Health Council of the Netherlands published a report to draw attention to the possibility of reducing the burden of disease and mortality of colorectal cancer by screening [van Veen 2001]. The report concludes that the introduction of a nation-wide screening program for colorectal cancer in the general population should be seriously considered. Before any screening program is introduced, however, several questions should be answered regarding, amongst others, the screening strategy, the compliance rate, the organization of screening and quality assurance and monitoring of screening. Furthermore, the impact of screening and surveillance on the capacity of endoscopic screening should be investigated. The author recommends that these questions be answered by empirical and model-based research. The minister subsequently informed the parliament that more research should be conducted before any decision about screening for colorectal cancer in the Netherlands could be made.

The COlorectal CAncer Screening Trial (Cocast) project group examined the possibilities of performing a randomized controlled trial in the Netherlands to determine the effectiveness and feasibility of colorectal cancer screening. The Cocast project group consists of gastroenterologists as well as researchers specialized in the evaluation of cancer screening. The most important question is whether endoscopic screening is preferable to FOBT screening with respect to (cost-) effectiveness and feasibility. The feasibility aspect relates to the compliance with and the capacity for a screening program. Colonoscopy, sigmoidoscopy and FOBT screening are the screening tests under consideration. However, colonoscopy requires even more endoscopic capacity than sigmoidoscopy screening and is therefore not regarded as feasible at this time. Furthermore, it is not possible to perform a randomized controlled trial with sufficient power to decide between endoscopic and FOBT screening based on differences in effects or cost-effectiveness. It is therefore more realistic to focus on FOBT and sigmoidoscopy screening and to perform implementation studies to investigate the compliance, the possibility of having screening endoscopies performed by nurse practitioners, the burden

of the test, possible complications for the participants and the organization and costs of screening. Furthermore, it may be worthwhile to investigate the test characteristics of immunochemical tests versus guaiac FOBT tests. It is not immediately clear whether a study of the compliance with FOBT screening can be combined with a study of the test characteristics of FOBT tests, as the compliance with FOBT screening is probably influenced by dietary restrictions. Guaiac tests usually require dietary restrictions, which is not the case for immunochemical tests.

Furthermore, it is not yet decided whether the participants should be randomized between the FOBT and the sigmoidoscopy implementation study. If participants are randomized, the results of the studies can be compared. If participants are not randomized, the FOBT implementation study can be performed in other regions than the sigmoidoscopy implementation study. This makes it possible to influence compliance by advertising in local newspapers etc. Furthermore, participants of the studies may be more willing to undergo the screening test if they are not informed about alternative screening tests.

If the result of the FOBT implementation study is that screening is feasible, an optimization study should be performed to compare the costs and effects of possible screening strategies. The optimal FOBT screening strategy should subsequently be introduced in the Netherlands. If the result of the sigmoidoscopy implementation study should show that screening is not feasible due to limited capacity or a low compliance rate, FOBT screening is to be preferred and the results of the UK sigmoidoscopy study are less important. Otherwise, as soon as the UK sigmoidoscopy screening confirms the effectiveness of sigmoidoscopy screening, both the effectiveness and the feasibility in the Netherlands will have been investigated and pilot programs based on sigmoidoscopy screening can be launched.

A possible colorectal cancer screening strategy in the Netherlands

Although an implementation study is needed to determine whether FOBT screening is feasible and an optimization study is needed to determine the optimal screening strategy, the following paragraphs dwell on a possible FOBT screening strategy. Immunochemical FOBT tests have better characteristics than guaiac FOBT tests: a higher sensitivity for cancer and the same specificity, approximately 98%, as unrehydrated FOBT tests. Furthermore, immunochemical tests do not require dietary restrictions. A drawback is that these tests are two to five times more expensive than guaiac tests. However, some of these tests, such as the latex agglutination test, can be processed automatically. This will reduce the personnel costs related to FOBT screening. Quantitative immunochemical tests have an advantage over qualitative immunochemical tests because the cut-off point for positivity can be chosen and optimized. Finally, the immunochemical test appears to have a higher sensitivity for large adenomas than the guaiac tests. In conclusion, an immunochemical test with a high specificity of at least 98% and reasonable unit costs would seem to be the preferred FOBT test.

Most randomized controlled trials used biennial FOBT screening. This is probably also the preferable interval for FOBT screening in the Netherlands. Shortening the interval to one year would introduce many more false-positive findings and would increase the

demand for colonoscopy even more. Furthermore, the impact of reducing the screening interval on the mortality reduction may be smaller than expected due to systematic false-negative test results (Chapter 3). If the results of immunochemical FOBT screening are more favorable than the results of unrehydrated guaiac FOBT screening, increasing the screening interval to 3 years may even be considered. This will decrease the capacity needed for diagnostic follow-up of diagnostic tests and will decrease the number of colonoscopies induced by false-positive test results. However, an optimization study should be performed to assess the optimal screening test (including the cut-off point), screening interval and age range for FOBT screening in the Netherlands.

The results of the randomized controlled trials that use sigmoidoscopy screening are expected in approximately 7 years. If sigmoidoscopy is effective in reducing mortality, and the cost-effectiveness is comparable to or more favorable than FOBT screening, and implementation studies show that sigmoidoscopy screening in the Netherlands is feasible, replacing the FOBT screening program by a sigmoidoscopy screening program or adding sigmoidoscopy to the program are both options to be considered. It is important that the burden of the sigmoidoscopy is as low as possible for the individual. This may imply having to prepare the patient for sigmoidoscopy in the hospital shortly before the test is performed, rather than at home. Furthermore, the capacity for sigmoidoscopy should be enlarged by training nurse endoscopists.

General conclusions

- The MISCAN-COLON model is a useful tool for the analysis of screening and surveillance studies and for the evaluation of screening strategies.
- A wide variation is seen among the different models regarding the assumptions on the adenoma dwell time and the percentage of colorectal cancers that originate from adenomas.
- Screening for colorectal cancer using FOBT tests reduces colorectal cancer mortality and is cost-effective.

Recommendations for screening and treatment of adenoma patients in the Netherlands

In this thesis, several recommendations for screening and treatment of adenoma patients have been formulated. The following is a summary.

- FOBT screening: Perform an implementation study to investigate the acceptability and the practical feasibility in the Netherlands. Perform an optimization study for FOBT screening in order to decide which FOBT screening strategy should be introduced in the Netherlands. Introduce FOBT screening in the Netherlands as soon as these studies show that it is feasible (Chapter 8).

- Sigmoidoscopy screening: Perform an implementation study to investigate the acceptability and the practical feasibility of sigmoidoscopy screening in the Netherlands. Do not introduce large-scale sigmoidoscopy screening until the results of the UK sigmoidoscopy trial are available. Perform an optimization study for sigmoidoscopy and FOBT screening if the results of the UK sigmoidoscopy trial are favorable and the implementation study has shown that sigmoidoscopy screening is feasible. Introduce sigmoidoscopy screening only if these studies show that it is feasible and that it is to be preferred to FOBT screening (Chapter 8).

- Colonoscopy screening: Colonoscopic screening should not be introduced. It is considered not feasible due to the large endoscopic capacity needed (Chapter 8).

- Treatment of adenoma patients: Perform a complete initial colonoscopy in patients with adenomas and remove all detected adenomas (Chapter 7). Offer adenoma patients regular surveillance colonoscopy according to the recent (2002) CBO-guidelines (Chapter 8).

Recommendations for further research

In the previous chapters, suggestions for further research have been formulated, which can be summarized in the below.

In the field of MISCAN-COLON parameter optimization

- Perform a comparison of the MISCAN-COLON model with other models for the cost-effectiveness analysis of colorectal cancer screening. This will provide more insight in the difference between the models and indicate on which aspects the models disagree (Chapter 8).
- Perform MISCAN-COLON studies by comparing observed and simulated results of empirical studies on endoscopic screening and surveillance. Important empirical studies in this respect are the CoCap study and the Health Professionals data. Furthermore, the National Polyp Study optimization study will be extended by the modeling of advanced adenomas (adenomas of size ≥1cm, villous histology, or high-grade dysplasia). This will enhance the precision of the natural history assumptions in the MISCAN-COLON model (Chapter 8).

In the field of surveillance of adenoma patients

- Study patient records of a selection of adenoma patients in the Netherlands that were diagnosed with colorectal cancer in the first years since adenoma diagnosis in order to find explanations for the high colorectal cancer incidence in the first years after adenoma diagnosis (Chapter 7).
- Develop a nation-wide endoscopy database in the Netherlands to be able to investigate which adenoma patients are at low risk for colorectal cancer and do not require colonoscopic surveillance (Chapter 8).

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Summary

Introduction

Colorectal cancer is a major public health problem in many countries. In 1997, approximately 8,500 new cases of colorectal cancer were diagnosed in the Netherlands and more than 4,000 individuals died from this disease. Screening for colorectal cancer in the general population has the potential to save lives. Potential screening tests are the fecal occult blood test (FOBT), colonoscopy and sigmoidoscopy. FOBT tests detect blood in stool from bleeding asymptomatic colorectal cancer or large adenomas. Sigmoidoscopy and colonoscopy are both endoscopic tests that visualize the colorectal tract. If adenomas, precursors of cancer, are detected at the screening test, they can be removed immediately. It is recommended that patients with removed adenomas undergo regular colonoscopic surveillance. In this thesis, aspects of colorectal cancer screening and of colonoscopic surveillance (follow-up) of adenoma patients are studied by analysis of relevant data and with the use of the MISCAN-COLON model.

The MISCAN-COLON model

The MISCAN-COLON model is used to estimate the costs and effects of colorectal cancer screening and surveillance of adenoma patients and to test hypotheses about the natural history of colorectal cancer and the impact of screening. The model is described in detail in Chapter 2. The MISCAN-COLON model is a micro-simulation model that simulates a large number of fictitious individual life histories. In each life history, several colorectal lesions can emerge. Next, screening for colorectal cancer is simulated, which will change some of the life histories. The changes in the individual life histories constitute the effect of screening. The effects of alternative screening policies can be compared by applying them to identical life histories. The model can also be used to estimate the effect of surveillance of adenoma patients. The three main uses of the model are analysis of data of population studies in the field of screening and surveillance of adenoma patients, testing of hypotheses about the natural history of adenomas and colorectal cancer, and evaluation of screening policies.

FOBT-screening

Several model studies have been published in which the effect of FOBT screening strategies were estimated that were not studied in population-based studies. All these models assumed that every cancer in the population has an equal chance to bleed at a particular moment. This assumption has been questioned, because part of the preclinical cancers may never bleed, thus giving rise to systematic false-negative test results. A research question addressed in this thesis is: *What is the impact of systematic negative results on the colorectal cancer mortality reduction achieved by FOBT-screening?*

It is concluded that systematic false-negative test results strongly impact on the estimated effect of FOBT screening if the screens are performed annually (Chapter 3). The impact of systematic false-negative test results is smaller in case of biennial screening. It

is unlikely that systematic negative test results played an important role in the Minnesota Colon Cancer Control Study (Chapter 8).

Sigmoidoscopy screening

Although the effectiveness of sigmoidoscopy screening in reducing colorectal cancer mortality has not been demonstrated in a large randomized controlled trial, it is considered promising. Sigmoidoscopy screening seems expensive, because the test is expensive compared to FOBT, and because diagnostic colonoscopy is needed after a positive sigmoidoscopy. However, it is plausible that endoscopic screening reduces colorectal cancer incidence by the removal of adenomas. This will not only reduce colorectal cancer mortality, but will also induce savings in colorectal cancer treatment. A research question addressed in this thesis is: *Are the costs of sigmoidoscopy screening compensated by induced savings?*

The MISCAN-COLON model was used to predict costs and savings of screening in the U.S. population. It is concluded that it may well be that, in the United States, the induced savings as a result of sigmoidoscopic colorectal cancer screening completely compensate for the costs (Chapter 4). Whether savings will exceed costs mainly depends on the ratio of the unit cost of sigmoidoscopy to that of colorectal cancer treatment. In the Netherlands, the savings of sigmoidoscopy screening will not completely compensate the costs of screening (Chapter 8).

Natural history of the adenoma-carcinoma sequence

The effectiveness of endoscopic screening and surveillance of adenoma patients will largely depend on the natural history of the adenoma-carcinoma sequence. However, it is not possible to observe this sequence directly, because adenomas and colorectal cancer are treated upon detection. The natural history of the adenoma-carcinoma sequence can indirectly be studied by investigating which assumptions on the adenoma-carcinoma sequence best explain observations in endoscopic screening studies and studies of surveillance in patients who had adenomas removed during endoscopy. An important study in this respect is the National Polyp Study. A research question addressed in this thesis is: *What natural history assumptions best explain the National Polyp Study results?*

We could only explain the high observed adenoma detection rates at surveillance and the low observed colorectal cancer incidence in the National Polyp Study by assuming a high incidence rate of adenomas accompanied by regression of adenomas (Chapter 5).

Colorectal cancer risk in adenoma patients

It is common that adenoma patients undergo complete colonoscopy in order to detect and remove all adenomas. However, some adenomas are missed at the initial colonoscopy, and new adenomas may develop at significant rates. Therefore, adenoma patients are recommended to be surveilled regularly by colonoscopy. Surveillance (follow-up) is considered an essential aspect in a screening strategy, as endoscopic, and to a less extent, FOBT screening can detect patients with adenomas. Surveillance should not be performed too frequently, because colonoscopies are expensive and involve complication risks. The optimal surveillance interval should depend on the colorectal cancer risk in adenoma

patients after initial polypectomy. Published risk estimates vary widely. The last research question addressed in this thesis is: *What is the colorectal cancer risk in patients with removed adenomas?*

We analyzed data from the endoscopy department of the Slotervaart hospital, Amsterdam, the Netherlands, and we performed a literature search that identified 5 other studies on relative colorectal cancer risk after colonoscopic polypectomy (Chapter 6). Surveillance was performed in all studies. The results of the Slotervaart study and the literature search were combined in a review study. The review shows that the colorectal cancer risk in the first years after polypectomy in selected adenoma patients who undergo high-quality initial colonoscopy, polypectomy and regular surveillance does not exceed the risk in the general population. It is suggested that the risk for patients with non-sessile adenomas is lower than in the general population. These results support lengthening of the surveillance interval to 5 years for most adenoma patients.

In the studies in Chapter 6, patients had undergone complete initial colonoscopy or incomplete initial colonoscopy followed by (negative) barium enema. In unselected adenoma patients, the colorectal cancer risk after adenoma removal may be higher than in these studies, because the quality of the initial colonoscopy and colonoscopic surveillance is lower than in the selected centers. In Chapter 7, the colorectal cancer relative risk is estimated in actual clinical practice in a large unselected population of adenoma patients. The trend in colorectal cancer risk according to time since first adenoma removal was also estimated. To this purpose, the nation-wide PALGA registry is used to investigate the colorectal cancer incidence in all 78,473 patients who had adenomas diagnosed between 1 January 1988 and 1 October 1998 in the Netherlands. The study shows that, with the current polypectomy and surveillance practice, adenoma patients have a significantly higher colorectal cancer risk than the general population, the incidence ratio being 1.5 (1.4-1.6) when the first year since first adenoma removal is excluded. The incidence ratio declined from 2.8 (2.5-3.1) in the second year after first adenoma removal to 0.9 (0.6-1.2) in year 9-11. This trend is the opposite of what was expected after adenoma removal. It is hypothesized that the high cancer incidence in the first years after polypectomy, even until the fifth year after adenoma removal, is caused by cancers missed during the diagnostic process. The hypothesis is supported by the fact that the results are consistent with a colonoscopic sensitivity for cancer of approximately 90%. Further evidence for the "missed cancers" concept may lead to modified clinical guidelines for diagnostic work-up of suspected colorectal cancer patients.

General conclusions

- The MISCAN-COLON model is a useful tool for the analysis of screening and surveillance studies and for the evaluation of screening strategies.
- A wide variation is seen among the different models regarding the assumptions on the adenoma dwell time and the percentage of colorectal cancers that originate from adenomas.
- Screening for colorectal cancer using FOBT tests reduces colorectal cancer mortality and is cost-effective.

Recommendations for screening and treatment of adenoma patients in the Netherlands

- FOBT screening: Perform an implementation study to investigate the acceptability and the practical feasibility in the Netherlands. Perform an optimization study for FOBT screening in order to decide which FOBT screening strategy should be introduced in the Netherlands. Introduce FOBT screening in the Netherlands as soon as these studies show that it is feasible (Chapter 8).

- Sigmoidoscopy screening: Perform an implementation study to investigate the acceptability and the practical feasibility of sigmoidoscopy screening in the Netherlands. Do not introduce large-scale sigmoidoscopy screening until the results of the UK sigmoidoscopy trial are available. Perform an optimization study for sigmoidoscopy and FOBT screening if the results of the UK sigmoidoscopy trial are favorable and the implementation study has shown that sigmoidoscopy screening is feasible. Introduce sigmoidoscopy screening only if these studies show that it is feasible and that it is to be preferred to FOBT screening (Chapter 8).

- Colonoscopy screening: Colonoscopic screening should not be introduced. It is considered not feasible due to the large endoscopic capacity needed (Chapter 8).

- Treatment of adenoma patients: Perform a complete initial colonoscopy in patients with adenomas and remove all detected adenomas (Chapter 7). Offer adenoma patients regular surveillance colonoscopy according to the recent (2002) CBO-guidelines (Chapter 8).

Samenvatting

Inleiding

In veel landen is dikke-darmkanker een belangrijk volksgezondheidsprobleem; zo werden in 1997 ongeveer 8.500 nieuwe gevallen van dikke-darmkanker geconstateerd in Nederland en meer dan 4.000 personen stierven aan deze ziekte. Bijna alle dikke-darmkankersterfte vindt plaats in de eerste 5 jaar na diagnose, waarbij de overleving sterk afhangt van het stadium bij diagnose. Ongeveer 90% van de patiënten met kankerstadium I overleeft de eerste 5 jaar na diagnose. Bij deze patiënten is de kanker alleen aanwezig in de oppervlakkige lagen van de darmwand. Van de patiënten met kankerstadium IV, waarbij de kanker al is uitgezaaid naar andere organen op het moment van diagnose, overleeft slechts 5% de eerste 5 jaar.

In het algemeen wordt aangenomen dat dikke-darmkanker zich ontwikkelt uit een bepaald type poliepen in de darm, zogenaamde adenomen. Ongeveer 30-50% van de ouderen heeft adenomen in de dikke-darm. Adenomen geven in het algemeen geen klachten en de meeste adenomen zullen niet tot kanker ontwikkelen. Het is ook mogelijk dat sommige adenomen weer vanzelf verdwijnen.

De sterfte aan dikke-darmkanker kan worden verminderd door dikke-darmkanker en/of adenomen vroeg op te sporen in de algemene bevolking. Het testen van personen zonder klachten om een ziekte vroeg op te sporen wordt screening genoemd. Mogelijke screeningtests voor dikke-darmkanker zijn: de fecal-occult-blood-test (FOBT), colonoscopie en sigmoidoscopie.

De FOBT-test detecteert onzichtbaar (occult) bloed in de ontlasting en is voornamelijk gericht op het vroeg ontdekken van kanker en grote adenomen, voorlopers van kanker. Er zijn verschillende typen FOBT-tests beschikbaar, meest gebruikelijk is de *guaiac* FOBT-test, bijvoorbeeld de Hemoccult II test. Een deelnemer aan FOBT-screening ontvangt thuis een FOBT-kit en neemt een faeces-monster gedurende 1 tot 3 opeenvolgende dagen. In de meeste FOBT-screeningprogramma's wordt er aan de deelnemers gevraagd om in deze periode hun dieet te beperken door bijvoorbeeld geen rood vlees te eten. De FOBT-kit wordt opgestuurd naar een laboratorium en daar wordt afgelezen of de test positief (wel occult bloed) of negatief (geen occult bloed) is. Deelnemers met een positieve FOBT-test worden uitgenodigd voor een colonoscopie waarbij de gehele darm wordt gecontroleerd op de aanwezigheid van adenomen en kanker. In een typisch FOBT-screeningprogramma wordt elk jaar of elke twee jaar een FOBT-test aangeboden aan personen met een leeftijd van 50 jaar en ouder.

Bij sigmoidoscopie en colonoscopie, beide endoscopische tests, wordt de darm gevisualiseerd. De deelnemer aan screening wordt eerst voorbereid zodat de darm schoon is. De endoscopische test zelf wordt poliklinisch uitgevoerd en kan zowel kanker als adenomen ontdekken. Colonoscopie visualiseert de hele darm, terwijl sigmoidoscopie het distale deel, dat wil zeggen de endeldarm plus het laatste deel van de darm gezien vanaf de maag, visualiseert. Het distale deel van de darm bevat 40-60% van de adenomen en

kankers. Als adenomen, voorlopers van kanker, worden ontdekt tijdens de test dan kunnen ze direct worden weggehaald. Er is daarbij een klein risico op complicaties. Omdat bij colonoscopie pijnbestrijding nodig is en bij sigmoidoscopie niet, is het complicatierisico hoger bij colonoscopie. In de meeste richtlijnen wordt aanbevolen om sigmoidoscopie of colonoscopie elke 5 of 10 jaar uit te voeren, ongeveer vanaf de leeftijd 50 jaar. Sommige gastro-enterologen bevelen aan een eenmalige sigmoidoscopie of colonoscopie uit te voeren op 50 of 60-jarige leeftijd.

In dit proefschrift worden belangrijke aspecten van dikke-darmkankerscreening met FOBT en sigmoidoscopie en periodieke colonoscopische controle (follow-up) van adenoompatiënten bestudeerd door analyse van relevante gegevens, onder andere met behulp van het MISCAN-COLON model.

Het MISCAN-COLON model

Het MISCAN-COLON model kan worden gebruikt om de kosten en effecten van dikke-darmkankerscreening en periodieke controle (follow-up) van adenoompatiënten te schatten. Daarnaast kan het model worden gebruikt om hypothesen over het natuurlijk beloop van dikke-darmkanker en de impact van screening te testen. Het model wordt gedetailleerd beschreven in Hoofdstuk 2. Het MISCAN-COLON model is een micro-simulatiemodel dat een groot aantal fictieve individuele personen (levensgeschiedenissen) simuleert. In een gesimuleerde levensgeschiedenis kunnen één of meer poliepen en/of kankers in de dikke darm ontstaan. Na het simuleren hiervan wordt screening op dikke-darmkanker gesimuleerd in dezelfde levensgeschiedenissen. Dit zal sommige levensgeschiedenissen veranderen. Het effect van screening bestaat uit de veranderingen in de individuele levensgeschiedenissen. Het effect van verschillende screeningstrategieën kan worden vergeleken door ze toe te passen op dezelfde populatie van levensgeschiedenissen zonder screening. De drie belangrijkste gebruiksmogelijkheden van het model zijn: analyse van data van populatiestudies op het gebied van screening en periodieke controle van adenoompatiënten, het testen van hypothesen over het natuurlijk beloop van adenomen en dikke-darmkanker en de evaluatie van screeningstrategieën.

FOBT-screening

In verschillende studies in de algemene bevolking (populatiestudies) is bestudeerd in hoeverre FOBT-screening sterfte aan dikke-darmkanker vermindert. In elke studie is een keuze gemaakt voor bijvoorbeeld een type FOBT-test, de leeftijdsgroep die is uitgenodigd, het interval tussen twee screeningtests (screening-interval) enzovoort. Dit geheel van keuzes wordt de screeningstrategie genoemd. Als men de effecten van een andere screeningstrategie wil bepalen, dan is het wegens de duur en de kosten niet altijd mogelijk een nieuwe populatiestudie uit te voeren. Er wordt daarom vaak gebruik gemaakt van wiskundige modellen om de effecten van screeningstrategiëen te berekenen.

Er zijn verschillende wiskundige modellen gepubliceerd waarmee de effecten van FOBT-screeningstrategieën kunnen worden berekend. In al deze modellen is aangenomen dat alle dikke-darmkankers bloed in de ontlasting kunnen veroorzaken. Deze veronderstelling is enige jaren geleden in twijfel getrokken, omdat het goed mogelijk is dat een deel van de kankers nooit bloed in de ontlasting veroorzaakt. Dit levert

systematisch fout-negatieve FOBT-testresultaten op, dat wil zeggen dat sommige kankers steeds opnieuw (systematisch) gemist zullen worden bij opeenvolgende screeningonderzoeken. Dit zal het effect van FOBT-screening verkleinen. Een onderzoeksvraag die wordt beantwoord in dit proefschrift is: *Wat is de invloed van systematisch fout-negatieve testresultaten op de reductie van dikke-darmkankersterfte door FOBT-screening?*

De conclusie is dat systematisch fout-negatieve testresultaten vooral van belang zijn bij jaarlijkse FOBT-screening (Hoofdstuk 3). Verder is niet waarschijnlijk dat systematisch fout-negatieve testresultaten een belangrijke rol speelden in de Minnesota Study (Hoofdstuk 8).

Sigmoidoscopiescreening

Hoewel de effectiviteit van sigmoidoscopiescreening in het verminderen van dikke-darmkankersterfte nog niet is aangetoond in een grote gerandomiseerde trial, wordt sigmoidoscopiescreening als veelbelovend beschouwd. Sigmoidoscopiescreening lijkt duur, omdat de test duur is ten opzichte van FOBT en omdat een diagnostische colonoscopie moet plaatsvinden na een positieve sigmoidoscopie. Echter, het is aannemelijk is dat sigmoidoscopiescreening het vóórkomen van dikke-darmkanker (incidentie) verlaagt door het verwijderen van adenomen. Dit verlaagt de sterfte aan dikke-darmkanker en levert ook besparingen in de behandeling van dikke-darmkanker op. Een onderzoeksvraag die wordt beantwoord in dit proefschrift is: *Worden de kosten van sigmoidoscopiescreening gecompenseerd door de besparingen die het oplevert?*

Het MISCAN-COLON model is gebruikt om deze kosten en besparingen in de Verenigde Staten te schatten. Uit de resultaten blijkt dat in de Verenigde Staten de besparingen van sigmoidoscopiescreening mogelijk even groot zijn als de kosten (Hoofdstuk 4). In hoeverre de besparingen de kosten van sigmoidoscopiescreening zullen compenseren hangt vooral af van de verhouding tussen de kosten van één sigmoidoscopie en de kosten van één behandeling van dikke-darmkanker. In Nederland zullen de besparingen van sigmoidoscopiescreening de kosten van screening niet geheel compenseren (Hoofdstuk 8).

Natuurlijk beloop van adenomen en dikke-darmkanker

De effectiviteit van zowel endoscopische screening als periodieke controle van adenoompatiënten hangt grotendeels af van het natuurlijk beloop van adenomen en kanker van de dikke darm. Het is niet mogelijk om dit direct te waar te nemen, aangezien adenomen en kanker direct worden behandeld na ontdekking. Het natuurlijk beloop kan indirect worden bestudeerd door te onderzoeken welke veronderstellingen de resultaten van endoscopische screeningstudies en studies naar het effect van periodieke controle van adenoompatiënten kunnen verklaren. Een belangrijke studie naar het effect van periodieke controle van adenoompatiënten is de National Polyp Study. Een onderzoeksvraag die wordt beantwoord in dit proefschrift is: *Welke veronderstellingen over het natuurlijk beloop verklaren de resultaten van de National Polyp Study?*

Hiertoe werd het waargenomen percentage patiënten met adenomen bij controle-colonoscopieën en het aantal kankergevallen in de National Polyp Study vergeleken met

de gesimuleerde uitkomsten van het MISCAN-COLON model (Hoofdstuk 5). Verschillende modelvarianten werden onderzocht om veronderstellingen te vinden die aansluiten bij de resultaten van de National Polyp Study. Het hoge percentage patiënten met adenomen bij controle-colonoscopie en het lage aantal kankergevallen in de National Polyp Study kunnen alleen verklaard worden door te veronderstellen dat zowel veel nieuwe adenomen ontstaan (hoge adenoomincidentie) als bestaande adenomen verdwijnen (regressie).

Risico op dikke-darmkanker in adenoompatiënten

Het is gebruikelijk dat adenoompatiënten tijdens, of kort na, de adenoomdiagnose een volledige colonoscopie ondergaan waarbij alle adenomen worden verwijderd (poliepectomie). Dit wordt de initiële colonoscopie genoemd. Omdat sommige adenomen echter worden gemist tijdens deze colonoscopie en er nieuwe adenomen kunnen ontstaan, wordt aanbevolen om adenoompatiënten regelmatig te controleren met colonoscopie. Controle van adenoompatiënten is een essentieel onderdeel van een screeningstrategie, omdat nieuwe adenoompatiënten zullen worden ontdekt tijdens screening, in het bijzonder tijdens endoscopische screening. De effectiviteit van een screeningstrategie wordt dus mede bepaald door de effectiviteit van de periodieke controle van adenoompatiënten. Controle-colonoscopieën moeten niet te vaak worden uitgevoerd, aangezien colonoscopieën duur zijn en gepaard gaan met een risico op complicaties. Het optimale controle-interval hangt sterk af van het dikke-darmkankerrisico in adenoompatiënten na de initiële colonoscopie. De gepubliceerde risicoschattingen lopen echter zeer uiteen. De laatste onderzoeksvraag die wordt beantwoord in dit proefschrift is: *Wat is het dikke-darmkankerrisico in patiënten bij wie adenomen zijn verwijderd?*

Hiervoor werd het dikke-darmkankerrisico in adenoompatiënten van de endoscopieafdeling van het Slotervaart Ziekenhuis, Amsterdam, Nederland berekend en deze resultaten werden gecombineerd met de resultaten van 5 andere studies naar het dikke-darmkankerrisico na poliepectomie (Hoofdstuk 6). Deze overzichtsstudie laat zien dat het dikke-darmkankerrisico in de eerste jaren na poliepectomie in geselecteerde adenoompatiënten met een hoge kwaliteit van de initiële colonoscopie, poliepectomie en controle-colonoscopieën niet hoger is dan het risico in de algemene bevolking. De resultaten wijzen erop dat het risico in patiënten met niet-sessiele adenomen lager is dan in de algemene bevolking. (Sessiele adenomen zijn adenomen zonder steel en deze poliepen zijn lastiger te verwijderen dan gesteelde adenomen.) Dit ondersteunt de verlenging van het controle-interval naar 5 jaar voor de meeste adenoompatiënten.

In de studies in Hoofdstuk 6 hadden de patiënten een complete initiële colonoscopie ondergaan of incomplete initiële colonoscopie gevolgd door een (negatief) bariumonderzoek. In ongeselecteerde adenoompatiënten zou het dikke-darmkankerrisico hoger kunnen zijn dan in deze studies, omdat de kwaliteit van de initiële colonoscopie en controle-colonoscopieën lager is dan in de geselecteerde centra waarin de studies uit Hoofdstuk 6 zijn uitgevoerd. Daarom is het dikke-darmkankerrisico ook berekend in een grote ongeselecteerde populatie van adenoompatiënten. Ook werd de trend in risico op dikke-darmkanker naar de tijd sinds de eerste verwijdering van een adenoom berekend. Het Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA) werd

gebruikt om het dikke-darmkankerrisico te berekenen in alle 78,473 patiënten bij wie adenomen werden gediagnosticeerd in Nederland tussen 1 januari 1988 en 1 oktober 1998. De studie concludeert dat, met de huidige poliepectomie- en controle-praktijk, adenoompatiënten een significant hoger risico op dikke-darmkanker hebben dan de algemene bevolking.

Het relatieve risico is 1.5 (1.4-1.6) als het eerste jaar na de eerste verwijdering van een adenoom is geëxcludeerd. Het relatieve risico daalt van 2.8 (2.5-3.1) in het tweede jaar na poliepectomie tot 0.9 (0.6-1.2) in het negende tot en met elfde jaar. Deze trend was tegenovergesteld aan de verwachte trend in dikke-darmkankerrisico naar tijd sinds poliepectomie. Het hoge risico in de eerste jaren na poliepectomie kan worden verklaard doordat kankers worden gemist tijdens het diagnostische proces. Deze hypothese wordt ondersteund door het feit dat de resultaten in overeenstemming zijn met een sensitiviteit van colonoscopie voor dikke-darmkanker van 90%. Verder bewijs voor dit concept van “gemiste kankers” kan leiden tot gewijzigde klinische richtlijnen voor het diagnostische proces van patiënten met klachten die gerelateerd zijn aan op dikke-darmkanker.

Overige conclusies

- Het MISCAN-COLON model is een nuttig instrument voor de analyse van screeningstudies en studies naar de periodieke controle van adenoompatiënten en de evaluatie van screeningstrategieën.
- Er zijn tussen de gepubliceerde dikke-darmkankermodellen grote verschillen in de veronderstellingen over de duur van het adenoomstadium en over het percentage van de dikke-darmkankers dat uit adenomen voortkomt.
- Screening op dikke-darmkanker met FOBT-tests vermindert de sterfte aan dikke-darmkanker en is kosteneffectief.

Aanbevelingen voor screening en behandeling van adenoompatiënten in Nederland

- Op het gebied van screening met FOBT: Voer een implementatiestudie uit om de acceptatiegraad en de praktische haalbaarheid van FOBT-screening te onderzoeken. Voer een optimalisatiestudie uit om te beslissen welke FOBT-test en screeningstrategie geïntroduceerd moeten worden in Nederland en introduceer FOBT-screening zodra bovenstaande studies hebben aangetoond dat dit haalbaar is (Hoofdstuk 8).

- Op het gebied van screening met sigmoidoscopie: Voer een implementatiestudie uit om de acceptatiegraad en de praktische haalbaarheid van sigmoidoscopiescreening te onderzoeken. Introduceer sigmoidoscopiescreening niet op grote schaal in Nederland totdat de resultaten van de sigmoidoscopiestudie in het Verenigd Koninkrijk bekend zijn. Als de resultaten van deze sigmoidoscopiestudie positief zijn en de bovenstaande implementatiestudie heeft aangetoond dat sigmoidoscopiescreening haalbaar is: Voer een vergelijkende studie voor sigmoidoscopie en FOBT-screening uit om te beslissen welke optimaal is. Introduceer sigmoidoscopiescreening alleen als bovenstaande studies hebben aangetoond dat het haalbaar is en dat deze strategie beter is of beter wordt geacht dan FOBT-screening (Hoofdstuk 8).

- Op het gebied van screening met colonoscopie: Screening met colonoscopie moet niet worden geïntroduceerd in Nederland. Screening met colonoscopie moet vooralsnog als niet haalbaar worden beschouwd omdat hiervoor een zeer grote capaciteit van endoscopie nodig is (Hoofdstuk 8).

- Op het gebied van behandeling van adenoompatiënten: Voer bij patiënten met adenomen een volledige colonoscopie uit en verwijder hierbij alle adenomen (Hoofdstuk 7). Bied adenoompatiënten controle met colonoscopie aan volgens de CBO-richtlijnen uit 2002 (Hoofdstuk 8).

Curriculum Vitae

Franka Loeve werd geboren op 24 april 1972 in Rotterdam. In 1990 behaalde zij het VWO-diploma aan de Christelijke Scholengemeenschap Comenius in Capelle aan den IJssel. In 1990 begon zij de studie Toegepaste Wiskunde aan de Universiteit Twente. In 1995 behaalde zij haar doctoraaldiploma bij de vakgroep Analyse, Discrete Wiskunde, Algebra en Meetkunde met als afstudeeronderwerp ‘Kennisgrafen, theorie en praktijk’. Van april 1995 tot februari 1996 werkte zij bij Cap Volmac en was zij gedetacheerd bij het Rijksinstituut voor Volksgezondheid en Milieu (RIVM), Laboratorium Luchtonderzoek. Van februari 1996 tot heden werkt zij bij het Instituut Maatschappelijke Gezondheidszorg van de Erasmus Universiteit Rotterdam. Hier doet zij onderzoek naar de kosten en effecten van screening op dikke-darmkanker met behulp van het MISCAN-COLON model. Daarnaast was zij lid van de werkgroep ‘Herziening Richtlijn Follow-up na Poliepectomie’. Zij heeft ook gewerkt aan het ontwerpen van een screeningtrial voor dikke-darmkanker in Nederland. Sinds maart 1999 werkt zij als consultant bij ORTEC bv te Gouda.