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

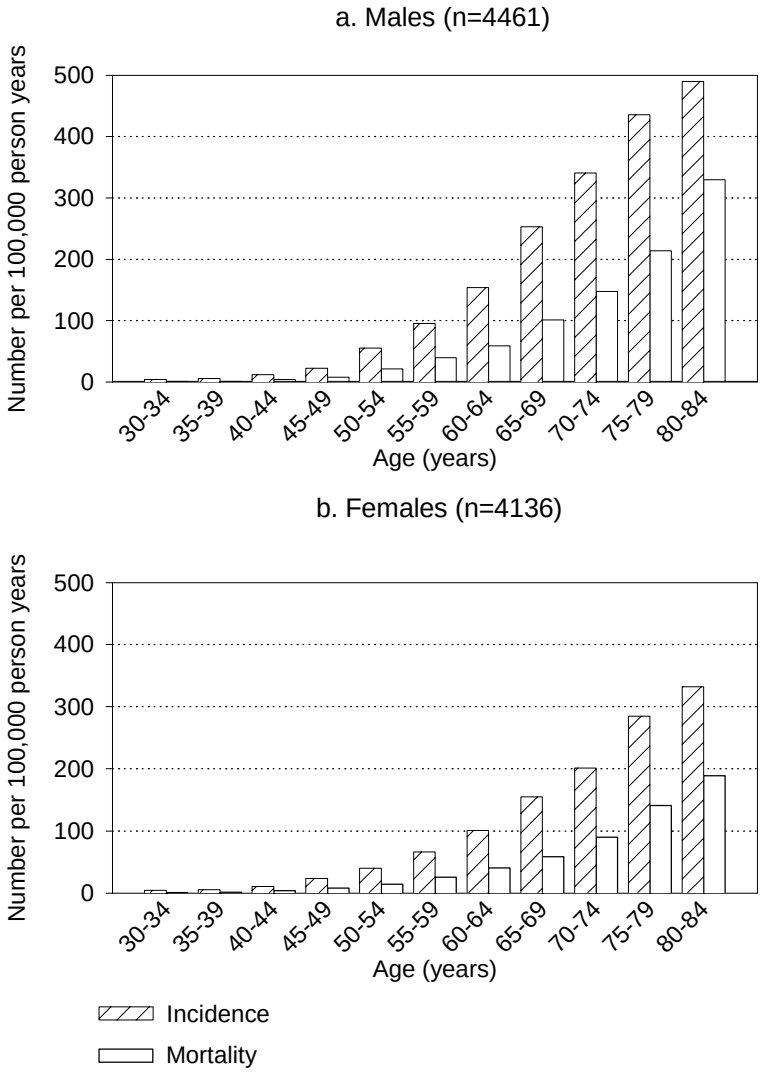

Figure 1.1 Colorectal cancer incidence and mortality in the Netherlands in 1997.

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

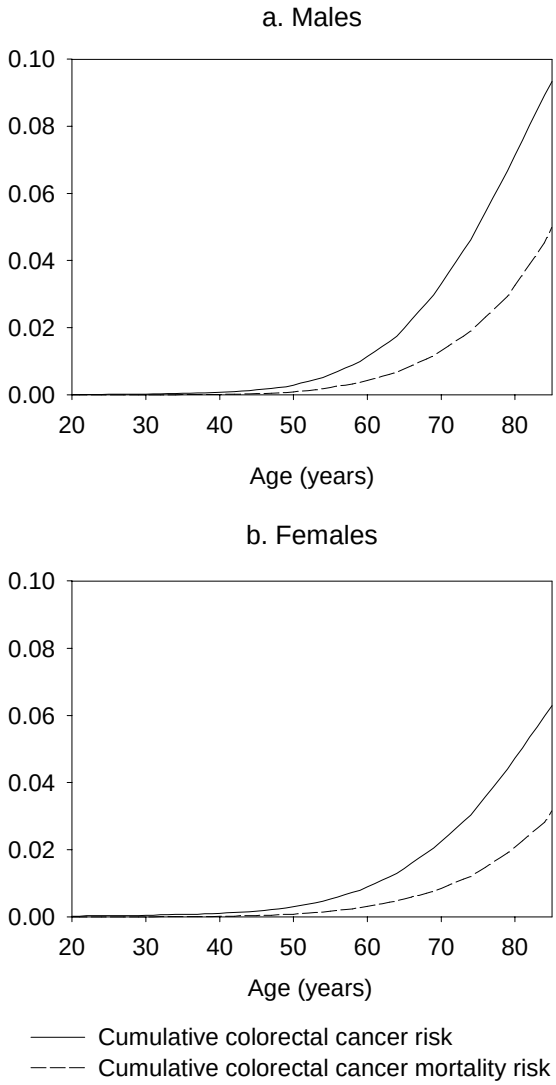

Figure 1.2 Cumulative colorectal cancer risk and colorectal cancer mortality risk in the Netherlands in 1997.

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

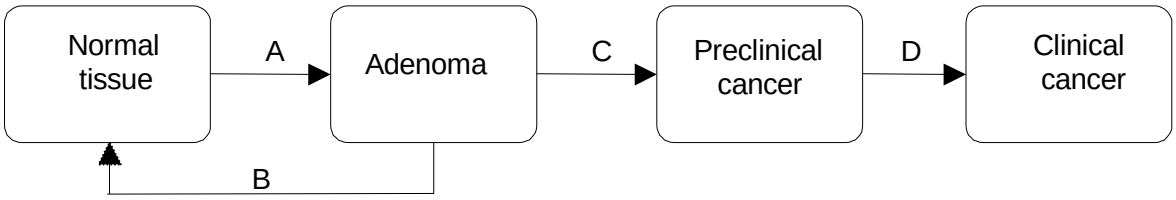

Figure 1.3 The adenoma-carcinoma sequence. A, onset of adenoma; B, regression of adenoma; C, onset of preclinical colorectal cancer; D, Diagnosis of colorectal cancer.

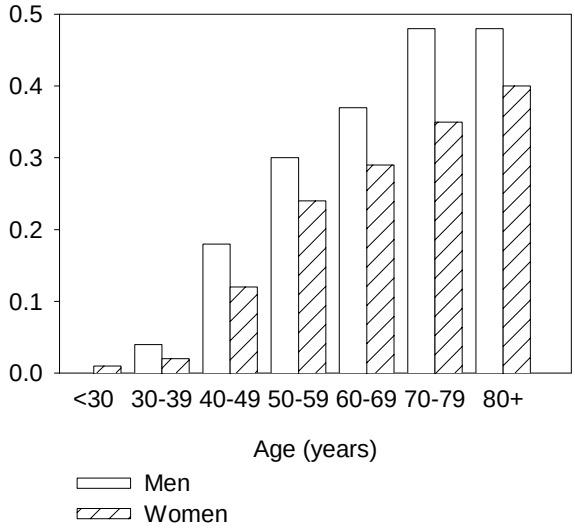

Figure 1.4 Estimated adenoma prevalence based on autopsy data [Koretz 1993].

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.

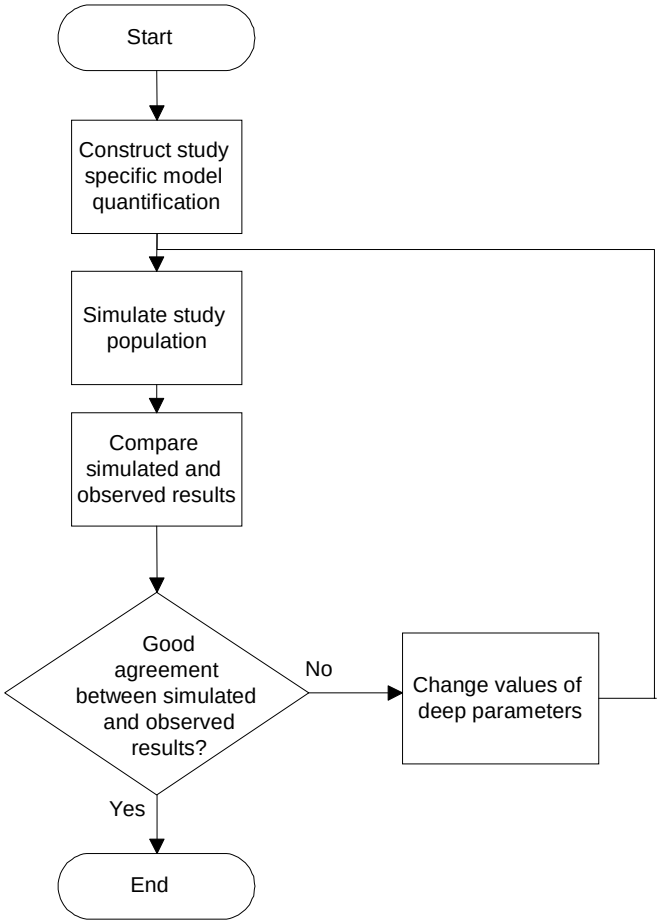

Figure 1.5 Parameter optimization with the MISCAN-COLON model: finding deep model parameters that fit the results of an empirical study by testing simulated results against observed results.

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.