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).