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).