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Aspects of Participation in Sigmoidoscopy Screening for Colorectal Cancer

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Till minne av pappa

ABSTRACT

Colorectal cancer is an important health problem due to a high morbidity and mortality but it is curable at an early stage and is therefore ideal for screening. Population-based screening of the average risk population using fecal occult blood testing has been demonstrated to decrease mortality. We are waiting for the results of randomized controlled trials evaluating sigmoidoscopy as a screening method. A high participation rate is a prerequisite for a screening program to be effective. The aim of this thesis was to evaluate the feasibility of sigmoidoscopy screening in a Swedish population with regard to compliance, findings and experiences among participants, factors associated with non-participation and possible self-selection among people participating.

We randomly selected two thousand men and women, aged 59-61, residing in the uptake areas of the University Hospitals of Uppsala and Lund, and invited them to a screening sigmoidoscopy. These individuals were randomized to being telephoned by a nurse to schedule an appointment or asked to call and make the appointment themselves. After the sigmoidoscopy, the participants were asked to describe their experiences in a questionnaire using VAS scales. Participants with a pathological finding were planned for a colonoscopy. To study background factors associated with non-participation, various registers were utilized to provide information on each individual's gender, country of birth, marital status, education, income, hospital contacts, place of residence, distance to screening center, and cancer within the family. All invitees were followed-up for nine years by means of record linkages to the Cancer- and Cause of Death Register.

Thirty-nine per cent (771/1986) participated. There was a statistically significant difference in participation between the centers (47% Uppsala, 30% Lund), but not between the methods of invitation. A total of 11% (88/771) underwent colonoscopy. Three subjects were found to have colorectal cancer and 46 (6%) had adenomas. Overall, the participants' answers to questions regarding self-perceived anxiety or discomfort were skewed towards low values on the VAS scale. The experience of pain and other discomfort could be explained by long examination time and anxiety during the procedure. Male gender (OR=1.27, 95% CI 1.03-1.57, relative to female), unmarried or divorced (OR=1.69, 95% CI 1.23-2.30 and OR=1.49, 95% CI 1.14-1.95, respectively, relative to married) and having an income in the lowest tertile (OR=1.68, 95% CI 1.27-2.23, relative to highest tertile) was associated with non-participation. The incidence of specific cancer and mortality outcomes tended to be higher among non-participants (e.g. colorectal cancer incidence [IRR=2.2, 95% CI 0.8-5.9] and mortality from gastrointestinal cancer [MRR=4.7, 95% CI 1.1-20.7]), compared those who participated. Relative to the matching general population, there was an overall increased risk of the studied outcomes among non-participants and a decreased risk among participants. For example, there was a 40% decreased risk of mortality from cancer (SMR=0.6 [0.3 to 0.97]) and a 50% decreased risk of all-cause mortality (SMR=0.5 [0.3 to 0.7]) among the participants.

Our results indicate that screening with sigmoidoscopy is feasible in colorectal cancer screening if, however, participation is not hindered by the sigmoidoscopy *per se*. Invitations must appeal to men, unmarried individuals and people with low socio-economic status. The higher incidences of specific cancers and mortality among non-participants may be related to self-selection. This self-selection could attenuate the cost-effectiveness of screening programs on a population level, but this effect could be counteracted by a high participation rate.

Key words: population-based, colorectal, neoplasms, polyps, mass screening, sigmoidoscopy, patient participation, patient experience, follow-up studies, mortality, registers

CONTENTS

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. ***Compliance and findings in a Swedish population screened for colorectal cancer with sigmoidoscopy***
Johannes Blom, Annika Lidén, Bengt Jeppsson, Lars Holmberg, Lars Påhlman
Eur J Surg Oncol 2002;28:827-31.*

II. ***Colorectal cancer screening with flexible sigmoidoscopy - participants' experiences and technical feasibility***
Johannes Blom, Annika Lidén, Jonas Nilsson, Lars Påhlman, Olof Nyrén, Lars Holmberg
Eur J Surg Oncol 2004;30:362-9.*

III. ***Towards understanding non-participation in sigmoidoscopy screening for colorectal cancer***
Johannes Blom, Li Yin, Annika Lidén, Anders Dolk, Bengt Jeppsson, Lars Påhlman, Lars Holmberg, Olof Nyrén
Submitted for publication

IV. ***A nine-year follow-up study of participants and non-participants in sigmoidoscopy screening: The importance of self-selection***
Johannes Blom, Li Yin, Annika Lidén, Anders Dolk, Bengt Jeppsson, Lars Påhlman, Lars Holmberg, Olof Nyrén
Submitted for publication

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ABBREVIATIONS

APC	Adenomatous Polyposis Coli
ARR	Absolute Risk Reduction
CI	Confidence Interval
CRC	ColoRectal Cancer
CTC	Computed Tomography Colonography
DCBE	Double Contrast Barium Enema
DCC	Deleted in Colorectal Carcinoma (gene)
FN	False Negative (test result)
FOBT	Fecal Occult Blood Testing
FP	False Positive (test result)
GIS	Geographic Information System
ICD	International Classification of Diseases
IRR	Incidence Rate Ratio
MRC	Magnetic Resonance Colonography
MRR	Mortality Rate Ratio
NNS	Number Needed to Screen
NNT	Number Needed to Treat
NPV	Negative Predictive Value
OR	Odds Ratio
PPV	Positive Predictive Value
RCT	Randomized Controlled Trial
RR	Relative Risk
SB-DNA	Stool-Based DNA
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
TN	True Negative (test result)
TP	True Positive (test result)
VAS	Visual Analog Scale

INTRODUCTION

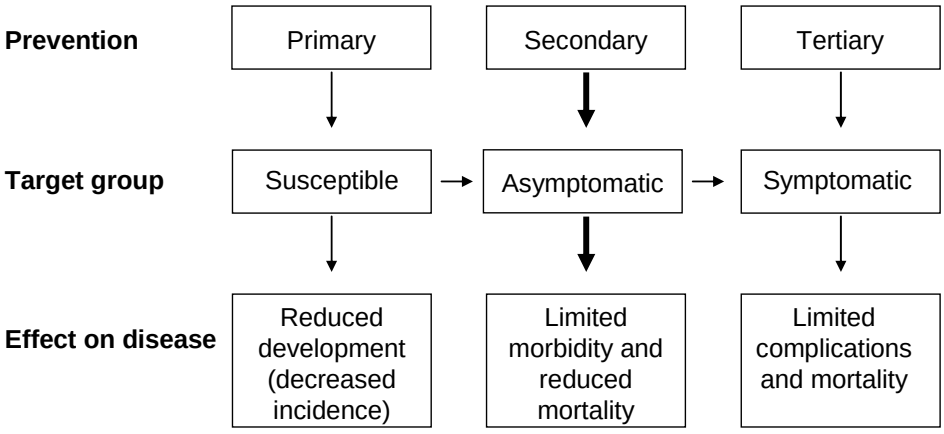
Screening and colorectal cancer

Primary prevention of colorectal cancer could be possible by eliminating risk factors associated with development of the disease. Therefore, efforts are directed towards susceptible individuals in whom the malignant transformation has not yet occurred. Changing diet, from red meat and fat in favor of fruits, vegetables and fibers, may reduce the risk of colorectal cancer development *(Potter et al. 2002)*. In secondary prevention, attempts are made to find the disease in an early, asymptomatic and readily curable stage with the aim of limiting morbidity and mortality. Screening is an example of secondary prevention (Figure 1).

The primary purpose of cancer screening is to reduce mortality from the disease in the population, but it also effects healthcare costs and quality of life *(Hakama et al. 2005)*. To be a suitable target for screening, the cancer has to be an important health problem. The cancer's natural history should be adequately understood and there should be an early detectable stage *(Wilson et al. 1968)*. Colorectal cancer is a relatively common disease and is the third most common cancer in Sweden (after prostate- and breast cancer) *(National Board of Health and Welfare [Socialstyrelsen] 2007a)*. Colorectal cancer has a high mortality (about 50% are expected to die of the disease *(Birgisson et al. 2005)*), but can be cured if detected at an early stage. Moreover, removal of the precursor stage, the adenomatous polyp (*Muto et al. 1975; Vogelstein et al. 1988*), has a documented protective effect against colorectal cancer development (*Winawer et al. 1993; Muller et al. 1995; Thiis-Evensen et al. 1999*). Consequentially, screening programs might also have the potential of decreasing the incidence of colorectal cancer in the future.

Colorectal cancer mass screening has gained acceptance in the United States of America, Australia, Austria, France, Germany, Italy, and Switzerland, and has been accepted in the reimbursement systems of these different countries *(Hakama et al. 2005)*.

Figure 1. Different preventions, target groups and expected effect on the disease.



Evaluation of a screening program

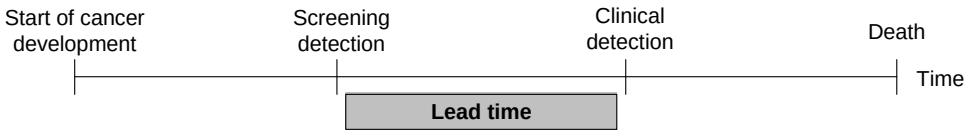
Effectiveness

The effectiveness of a screening program is the ability of the program to reduce the disease specific mortality. Survival is not a valid measure. The comparison of survival, e.g. in colorectal cancer, among screen-detected and clinically detected cases is difficult due to the possibility of bias:

Selection bias occurs when screened subjects and non-screened controls represent different population strata with differing colorectal cancer risks and in case-control evaluations when the cases who die from colorectal cancer and the surviving controls do not represent the same source population.

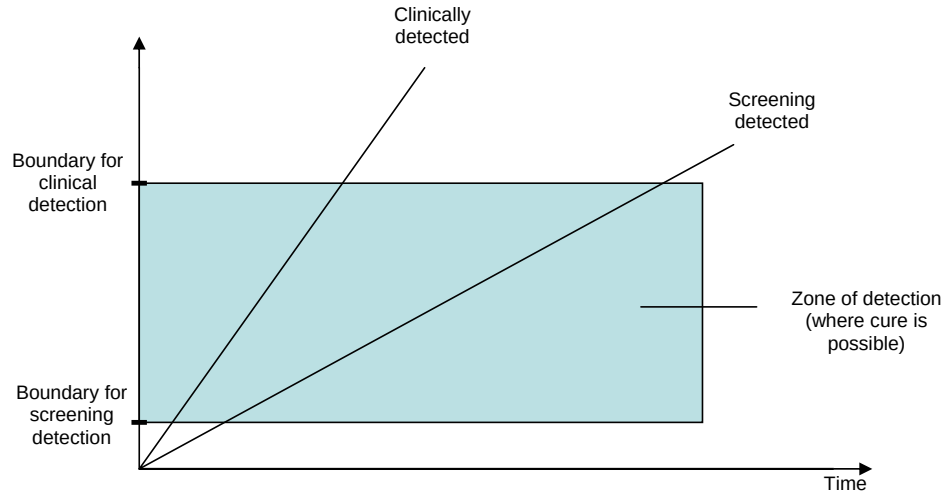
Lead time bias occurs when investigators fail to recognize that the earlier diagnosis adds time to the total survival time even if there is no change in the time of death (Figure 2).

Figure 2. Lead time bias. Earlier diagnosis gives longer total survival time.



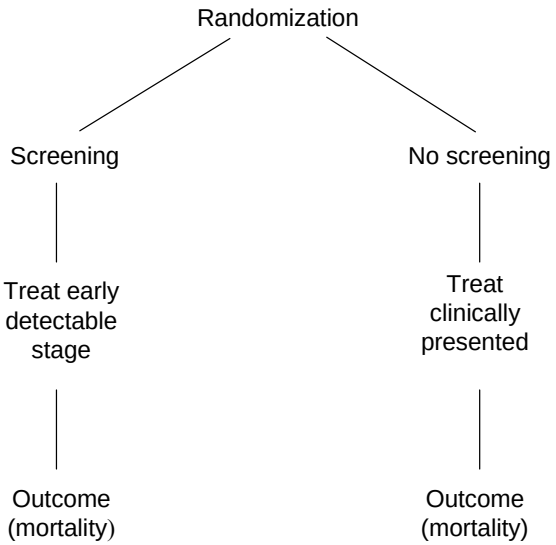
Length biased sampling is another pitfall that may result in a spurious survival advantage for tumors detected at screening compared to tumors that present clinically. Since slowly growing – and possibly less malignant – tumors take a longer time to pass the stage between being barely detectable with screening instruments and becoming clinically evident than do more aggressive tumors, the former type of tumor is more likely to be picked up by screening programs (Figure 3).

Figure 3. Length biased sampling. Screen-detected tumors are often slowly growing and possibly less malignant.



Hence, the only valid measure of the success of screening is a lower mortality in the screened group, preferably in a trial with random assignment of the screening scheme (Figure 4).

Figure 4. Design of a randomized controlled trial evaluating screening.



The screening test

The screening test offered should, since it will be used by people in the general population who – in the main – do not have the disease, be simple, free from unwanted side effects, easy to interpret and inexpensive *(Armitage 1997)*. Moreover, a high sensitivity and specificity is essential to limit the number of people who have the disease but are missed as well as those who are incorrectly diagnosed as having the disease.

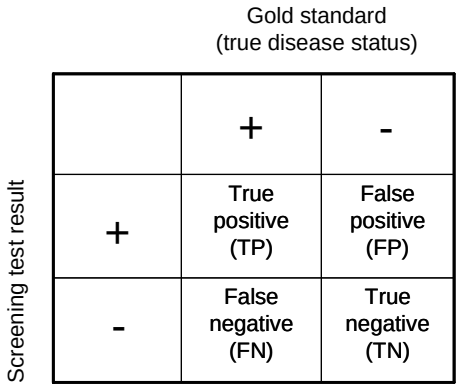


Figure 5. Calculations of accuracy of a screening test.

Sensitivity, Specificity and Predictive Values

Sensitivity

The sensitivity of a test is the test's ability to correctly classify people with the disease as "sick" – the proportion of people with the disease who have a positive test result. It is generated with the formula TP/TP+FN, where TP is the number of true positives and FN is the number false negatives, i.e. people with the disease who have a negative test result (Figure 5). With a high sensitivity, there are few false negative results, and thus few people with the disease are missed.

Specificity

The specificity of a test is the test's ability to correctly classify people without the disease as healthy – the proportion of healthy people who have a negative test result. It is generated by TN/TN+FP, where TN is the number of true negatives and FP is the false positives. With a high specificity of the test, there are few false positive results, and thus few people are incorrectly classified as having the disease.

Sensitivity and specificity are useful when we want to select a test to use in screening, but are of limited use in the individual patient – they only tell us how accurate a test is in confirming if the patient has a disease or not (when we actually already know). The predictive values on the other hand, may be used to estimate the probability of the disease in a patient.

Predictive Values

The predictive values of a test are determined not only by the sensitivity and specificity of the test, but also by the prevalence (the number of subjects with the disease in the population at that point in time).

Positive predictive value (PPV)
The PPV is the probability that a positive test will be correct – the probability of a person to have the disease if they have a positive test result. It is generated by TP/TP+FP. A test with high specificity (few FP) has a high PPV. Thus it is less likely for a person with a positive test to be healthy.

Negative predictive value (NPV)
The NPV is the probability that a negative test will be correct – the probability of a person to be healthy if they have a negative test result. It is generated by TN/TN+FN. A test with high sensitivity (few FN) has a high NPV. Thus it is less likely for a person with a negative test to have the disease.

Usually, when increasing the sensitivity of a test, e.g. by rehydration of the guaiac-based Fecal Occult Blood Test (FOBT) used in colorectal cancer screening *(Winawer et al. 2003)*, most often false positive (FP) rates will also increase, i.e. the specificity will decrease.

In screening, a test with low specificity is not feasible since many people in the population without the disease will have a positive test (Table 1). False positive results generate anxiety, cost due to unnecessary follow-up with different diagnostic procedures, and even morbidity or mortality due to complications from unnecessary diagnostic or therapeutic measures.

Table 1. The test results of screening 100,000 subjects for colorectal cancer (CRC) using a test with 95% sensitivity and 99% specificity. We know that 100 (0.1%) subjects have CRC (by using gold standard)

	Cancer	**No cancer (healthy)**	
Positive test	95	999	
Negative test	5	98,901	
Total	100	99,900	100,000

Even with a specificity of as high as 99%, there will be approximately 1000 false positive tests in this population. Only approximately 1 in 10 subjects with a positive test have the disease (PPV~10%). With a specificity of 95%, the number of false positive test would be approximately 5000 (TN=0.95 x 99,900; FP=99,900-TN).

The importance of prevalence

The prevalence depends on the incidence of the disease (the number of subjects getting "sick" during a period of time) and the duration of the disease. In the general population, the prevalence of most diseases is low, e.g. in Sweden approximately 3% for overall cancer *(Stenbeck et al. 1999)*.

In cancer screening, it is not primarily people with already established disease we aim for, but people in the curable, preclinical, detectable phase – "the zone of detection" (Figure 3). If the target group for screening sigmoidoscopy is 55-64 year old people, they account for approximately 1,200,000 people of the Swedish population *(Statistics Sweden [SCB] 2005)*. There were 654 diagnosed cancers within the reach of the sigmoidoscope (descending- and sigmoid colon and rectum) in this age group in 2005 *(National Board of Health and Welfare 2007a)*. Let us assume that "the zone of detection" is two years. This gives, hypothetically, 654 x2=1308 detectable cancers and a prevalence of just over 0.1% (1,300/1,200,000). This is a simplified example, where we do not consider the potential of sigmoidoscopy to find people with high risk of proximal cancers (see below). As a consequence, although using a test with high sensitivity and specificity in colorectal cancer screening of the average-risk population, the positive predictive value of the test will be low, but it will increase in older age groups where the prevalence of the disease is higher.

Two fictitious examples are described in Table 2 and 3:

Table 2. The results of screening 100,000 subjects for colorectal adenomas with a prevalence of 10,000 (10%) using a test with 95% sensitivity and specificity

	Adenoma ("sick")	**No adenoma (healthy)**	
Positive test	9,500	4,500	
Negative test	500	85,500	
Total	10,000	90,000	100,000

The PPV of the test is 68% (9500/[9500+4500]).

Table 3. The results of screening 100,000 subjects for colorectal cancer with a prevalence of 100 (0.1%) using a test with 95% sensitivity and specificity

	Cancer	**No cancer**	
Positive test	95	4,995	
Negative test	5	94,905	
Total	100	99,900	100,000

The PPV of the test is 2% (95/[95+4995]).

Compliance

To make people participate in screening, the screening test must also be acceptable to the population being screened. The proportion of individuals offered a test who actually complete it is referred to as compliance *(Armitage 1997)*. The compliance to a screening program is a major determinant of the programs effectiveness *(Faivre et al. 2002)* (see below).

Cost-effectiveness

To measure the cost-effectiveness of a screening program, one has to make assumptions about the duration of the early, asymptomatic, curable stage of the disease, the effectiveness and adverse effects (including morbidity and costs due to people incorrectly diagnosed with the disease) with each screening test and take into consideration the expected compliance. Low compliance in a screening program will not only hamper the mortality reduction achieved, but also the cost-effectiveness of the program.

This thesis deals with the feasibility of sigmoidoscopy as screening test for colorectal cancer with focus on different aspects of participation. We do not have the possibility to evaluate the effectiveness of sigmoidoscopy on mortality reduction. This topic of major importance must be evaluated in a randomized controlled trial (see above).

COLORECTAL CANCER SCREENING

Effectiveness

In an updated review, combining results from four randomized controlled trials (RCTs), a 16% reduction in colorectal cancer mortality has been demonstrated with screening using FOBT *(Hewitson et al. 2007)* (Table 4). The degree of mortality reduction with the FOBT depends on the compliance, the screening frequency (annual or biennial), the number of screening rounds the subjects participate in, and compliance with the diagnostic follow-up colonoscopy of a positive test. This is why, as opposed to opportunistic screening, a rigid organization with a call-recall system and quality assurance is obligate for a screening program to be effective *(Faivre et al. 2002)*. So, even with the reduction in colorectal cancer (CRC) mortality in ideal conditions in randomized controlled trials (efficacy), the effectiveness of screening to reduce mortality in the average-risk population in routine screening (normal conditions), must be evaluated before introducing screening programs as a public health policy.

To avoid selection bias when evaluating randomized controlled trials, it is also important to include those who decline participation (intention-to-treat analysis). The number needed to treat (NNT) is often used to evaluate treatment and is interpreted as the number of persons needed to be treated to prevent a particular event. It is calculated as the reciprocal of the absolute risk reduction (1/ARR) *(Wen et al. 2005)*, where the ARR is the absolute value of the difference in event rate (risk) between the control group and the treated group.

Instead of NNT, number needed to screen (NNS) is used in the evaluation of RCTs of screening, and is interpreted as the number of people who need to be offered screening (invited) to prevent one death (intention-to-screen). The results then reflect the efficacy of the screening method to reduce mortality among those invited to screening, and is often an underestimation of the efficacy of the screening test in those people who participate (actually being screened) *(Richardson 2001)*. The NNS for most screening programs are usually much higher than the number of people who actually have to participate to prevent one death. Hence, high participation in a screening program is very important to be able to evaluate its effect. Only those who participate can contribute to the mortality reduction achieved by the program and with low participation the number of deaths prevented will be few, and consequently the NNS will be very large *(Richardson 2001)*. While trying to estimate the real effect in those participating, an adjustment is sometimes made by dividing the effect generated in the intention-to-screen analysis by the proportion of participants *(Glasziou 1992)*. Like in breast cancer screening, it might be advantageous to inform the people invited to colorectal cancer screening of the estimates associated with actually being screened and to communicate the effect of the invitation to policy decisions *(The Swedish Organised Service Screening Evaluation Group 2006a)*.

To date, there is only one small randomized controlled trial published from Norway, demonstrating the impact of sigmoidoscopy screening in terms of reducing CRC incidence in an average risk population (Relative risk [RR]=0.2, 95% Confidence Interval [CI] 0.03-0.95, relative to no intervention), but the efficacy of reducing colorectal cancer mortality could not be assessed due to few observations (one and three deaths among screened and controls, respectively) *(Thiis-Evensen et al. 1999)*. Older case-control studies though, nested within observational cohorts, have indicated a protective effect

against mortality in colorectal cancer with sigmoidoscopy screening *(Newcomb et al. 1992; Selby et al. 1992)*. Since case-control studies compare mortality among screened subjects with mortality among matched controls (unscreened), the results are valid for an unrealistic 100% compliance *(Faivre et al. 2002)*. Speculatively though, the reduction of mortality in the population is estimated to be approximately 20% with a participation rate of 70% *(Atkin et al. 1993)*, 12% with a participation rate of 50% *(Cockburn et al. 1995)*, and a modest 5% with a participation rate of 30% *(Robinson et al. 1993)*.

Table 4. Comparison of four larger RCTs of colorectal cancer screening with FOBT included in a review by The Cochrane Collaboration *(Hewitson et al. 2007)*

RCT	Follow-up (yrs)	CRC deaths		RR*	ARR†	NNS‡
		Screened	Control			
Göteborg *(Haglind et al. 2005)*	15.5	252/34,144	300/34,164	0.84	0.0014	714
Funen *(Kronborg et al. 2004)*	17	362/30,967	431/30,966	0.84	0.0022	455
Nottingham *(Scholefield et al. 2002)*	11.7	593/76,466	684/76,384	0.87	0.0012	833
Minnesota *(Mandel et al. 1999)*	18	269/31,157	177/15,394	0.75	0.0029	345

* Relative Risk=the event rate (risk) in the control group/event rate in the screened group.
† ARR=event rate in control group – event rate in screened group.
‡ NSS=1/ARR.

The screening test

The American Cancer Society (ACS) recommends, starting at age 50, annual FOBT, sigmoidoscopy every five years or preferably the combination of both *(Smith R.A. et al. 2001; Winawer et al. 2003)*. Colonoscopy every 10 years or double contrast barium enema (DCBE) every five years are also recommended.

When we discuss the different colorectal cancer screening tests below, comparing the PPVs of the different tests is not appropriate. In literature, the PPVs of the different tests, except that for FOBT, are most often estimated in a very selective population with a very high prevalence of adenomas or cancer, and not applicable to the screening situation in an average risk population. For example, the PPV of Double Contrast Barium Enema (DCBE)

for polyps has been estimated to 87% in a population with a 100% prevalence of polyps *(Ott et al. 1983)*. This is just a way of demonstrating that the findings were only correctly classified as polyps in 87% of examinations, i.e. the other 13% were false positive.

Fecal Occult Blood Testing

Fecal Occult Blood Testing (FOBT) is to test the stool for mostly invisible, i.e. occult, blood. It has the advantage, compared to other screening methods, of being simple, safe and inexpensive. "FOBT-kits" usually contain a stool collection device and an analytical system based on either guaiac-peroxidase reaction or tests that detect heme porphyrine *(Starkey 2002)*. More advanced immunological tests (FITs) with higher sensitivity, but only a marginally increase in the false-positive rate, are also available *(Smith et al. 2006)*. Annual screening is recommended in the United States *(Winawer et al. 2003)*, although biennial screening has mostly been adopted in Europe *(Kewenter et al. 1994; Scholefield et al. 2002; Kronborg et al. 2004)*. Two samples from each of three consecutive stools should be examined *(Winawer et al. 2003)*. A positive test must be followed, not without risks, by a costly diagnostic examination of the entire colon, i.e. colonoscopy or sigmoidoscopy and double contrast barium enema (DCBE). One problem with FOBT, is that only lesions larger than 2 cm bleed consistently *(Macrae et al. 1982)* and, consequently, small pre-malignant lesions might be missed. Another problem is that red meat may give false positive tests *(Feinberg et al. 1990)* and dietary restrictions are often recommended for the more sensitive guaiac-based test *(Winawer et al. 2003)*. A restricted diet does not reduce the positivity rate of the older, less sensitive test, but could on the other hand reduce participation rates *(Pignone et al. 2001)*.

The sensitivity of a single FOBT is low, 30-50% *(Winawer et al. 2003)*, but with repeated testing in a program the sensitivity is higher *(Mandel et al. 1993)*. Despite a specificity of 95% *(Imperiale et al. 2004)*, the PPV of FOBT was less than 20% in the RCTs included in the updated systematic review by The Cochrane Collaboration *(Hewitson et al. 2007)*. The participation rate in the RCTs of FOBT in the review ranged from 60-78%.

Double Contrast Barium Enema

Double Contrast Barium Enema (DCBE) is a radiological method when first, after bowel preparation, barium-containing contrast is administered into the rectum and, secondly, air is insufflated. DCBE has been keenly recommended by some as an additional examination to sigmoidoscopy to cover the entire colon *(Mendelson et al. 1995; Cheong et al. 1998)*, but it has also been proposed as the only screening instrument every 5 years *(Ott 2000; Winawer et al. 2003)*. The major benefit of DCBE is that the entire colon is examined at much lower cost and risk than colonoscopy *(Ott 2000)*, with the disadvantage of lower sensitivity *(Smith G.A. et al. 2001)*. In case of a positive finding, a diagnostic endoscopy must still be performed. Another drawback is that DCBE is associated with relatively high doses of radiation *(Lampinen et al. 1999)*.

Depending on good bowel preparation and the meticulous interpretation by the radiologist, the sensitivity and specificity has been estimated to 80 and 95%, respectively, for polyps and cancers ≥ 1 cm *(Ott 2000)*.

There is a lack of published data on compliance in screening with DCBE. Speculatively, compliance in a screening program with DCBE may be low, since it has been described as the least utilized modality in a randomly selected population in the U.S. *(Yeazel et al. 2004)*.

Computed Tomography Colonography

Computed Tomography Colonography (CTC) is a novel technique where data from spiral CT scanner images are three-dimensionally reproduced to simulate the endoluminal views of colonoscopy; "virtual colonoscopy". Standard bowel preparation and air insufflation is used, but could be limited to per oral preparation in frail people *(Kealey et al. 2004)*. The actual examination is rapid *(Johnson et al. 1999)*, well tolerated *(Gluecker et al. 2003)*, and does not cause any major complications. Another positive aspect is the possibility of finding significant extra-colonic pathology *(Ng et al. 2004)*.

In a population of patients referred for a diagnostic or screening colonoscopy, the sensitivity of CTC was estimated to be 90% and the specificity 72% for polyps ≥ 1 cm *(Yee et al. 2001)*. CTC is not yet recommended for screening outside research settings due to lack of clinical studies in the average-risk population and understanding of its costs *(Winawer et al. 2003)*.

Magnetic Resonance Colonography

Magnetic Resonance Colonography (MRC) is another form of a "virtual colonoscopy" (see above), using the magnetic resonance imaging technique. The same bowel preparation as conventional colonoscopy is needed, but could be avoided by using fecal tagging *(Weishaupt et al. 1999)*. The benefit of MRC, as compared to CTC, is that no ionizing radiation is used. With repeated screening examinations, ionizing radiation could be a public health concern in the future *(Debatin et al. 2003)*. In MRC, though, the patients cannot have metallic implants.

High diagnostic accuracy for lesions >1 cm has been reported (sensitivity of 93% and specificity of 99%) in a small population (132 patients) referred for colonoscopy for exclusion of colorectal masses *(Luboldt et al. 2000)*. As with CTC, MRC, is an emerging technique and not yet well enough established.

Stool-Based DNA

It is believed that normal colorectal mucosa can develop into cancer by a series of alterations involving a precursor stage, the adenomatous polyp *(Muto et al. 1975; Vogelstein et al. 1988)*. A series of genetic events have been identified *(Fearon et al. 1990)*. Events involved are mutations in the APC (adenomatous polyposis coli)-gene leading to abnormal epithelial proliferation and mutations in the K-ras gene resulting in adenoma formation. A mutation of the DCC (deleted in colorectal carcinoma)-gene, followed by a mutation of the p53-gene, finally results in cancer development.

While testing stool for occult blood is rather unspecific, the identification of tumor-specific DNA, stool-based DNA (SB-DNA), can be an interesting concept in the future. The DNA is shed continuously and not intermittently as seen with blood. No dietary restrictions are needed. Moreover, the sampling technique obviates the need for handling stool *(Schroy III et al. 2005)*. Colorectal cancers, though, are genetically heterogeneous. The mutations in the APC-, K-ras- and p53-gene can be demonstrated in the stool, but from a screening point of view, multiple DNA markers are needed to detect a high percentage of the existing colorectal cancers *(Starkey 2002)*.

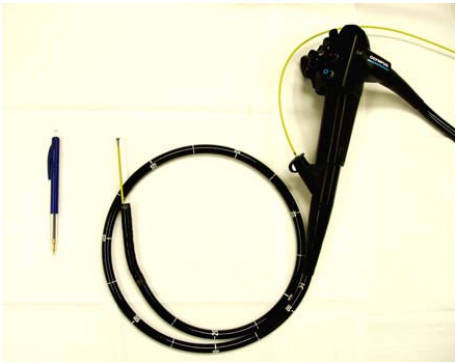
In a study of a panel of selected DNA markers in 33 patients with neoplasms and 28 controls, a sensitivity of 91% for cancer and 82% for adenomas ≥ 1 cm and a specificity of 93% was reported *(Ahlquist et al. 2000)*. Unfortunately, the results were not as promising in a larger study in the average-risk population (sensitivity 52% [lower for adenomas], specificity 94%) *(Imperiale et al. 2004)*. SB-DNA

testing has been shown to be preferred compared to FOBT and colonoscopy by asymptomatic subjects *(Schroy III et al. 2005)*.

Endoscopy

The main advantages with endoscopy (e.g. colonoscopy and sigmoidoscopy) are the direct visualization of the colon and, more importantly, the possibility of removing adenomatous polyps (adenomas) and obtaining tissue samples from suspected cancer lesions during the procedure (Figure 6).

Figure 6. Picture of an endoscope.



The adenomatous polyp

The prevalence of adenomas increases with age with a plateau at about 9% before 60 years *(Atkin et al. 1993)*. They are classified into tubular, tubulovillous (mixed) and villous adenomas according to their histological appearance and into containing either low-grade or high-grade dysplasia. The severity of dysplasia increases with degree of villous nature and size. Up to about 10% of adenomas will develop into colorectal cancer *(Waye 1986)* and the risk increases with size *(Nusko et al. 1997)*.

Colonoscopy

The entire colon can be inspected with a colonoscopy after bowel cleansing. Another benefit is the minimization of a secondary investigation; people with a positive screening test using other methods need a diagnostic colonoscopy. There is also, owing to the need for only one single session, a reduction in the indirect costs by decreasing the time needed away from work in order to participate *(Swaroop et al. 2002)*. Moreover, colonoscopy is recommended as screening test every 10 years, as compared to FOBT annually or sigmoidoscopy every five years *(Winawer et al. 2003)*. Colonoscopy is, however, relatively expensive in terms of direct costs, uncomfortable, and carries a small risk of severe complications such as bleeding and perforation *(Dafnis et al. 2001)*.

Colonoscopy is often used as "gold standard" in the estimation of the accuracy of new techniques. Still, the accuracy of colonoscopy is dependent on the experience of the endoscopist and the thoroughness of the bowel preparation. A sensitivity of 97% for cancer and 91% for polyps ≥ 1 cm has been reported *(Smith G.A. et al. 2001)*. As with DCBE, there is a lack of data on compliance with colonoscopy as the screening test, but the low compliance with colonoscopy follow-up of adenoma and CRC patients is discouraging *(Mulder et al. 2007)*.

Sigmoidoscopy

Sigmoidoscopy shares the benefits of colonoscopy inasmuch as the bowel is directly visualized and adenomas can be removed, but only in the approximately 60 cm of the most aboral colorectum. A rectal enema, applied on the day of the examination, is claimed to be sufficient bowel preparation *(Cockburn et al. 1995)*. Sigmoidoscopy is not as expensive as colonoscopy and is easier to perform, routinely in less than 10 minutes *(Zuber 2001)*. Sigmoidoscopy is recommended as screening instrument every five years, with or without annual FOBT *(Winawer et al. 2003)*. The screening interval is shorter than for colonoscopy due to lower

sensitivity even in the area examined. This is because of the less effective bowel preparation used and the varied experience of the endoscopists *(Winawer et al. 2003)*. Incomplete sigmoidoscopies in up to 25% of the examinations have been reported in literature *(Painter et al. 1999; Stewart et al. 1999)*.

Screening sigmoidoscopy has also been suggested as effective in finding people with high risk of advanced proximal neoplasm (adenoma ≥ 1 cm, villousness or dysplasia or invasive cancer) *(Atkin et al. 1993)*, but it is controversial if a colonoscopy of the entire colon should follow with detection of any neoplasm found at sigmoidoscopy – it is an individual clinical decision *(Winawer et al. 2003)*. Factors associated with increased risk of proximal lesions are villous histology and size ≥ 1 cm, multiple adenomas, older age, and a family history of colorectal cancer *(Levin et al. 1999; Imperiale et al. 2000; Lieberman et al. 2000)*. With sigmoidoscopy defined as examination of the rectum and the sigmoid colon during colonoscopy, a sensitivity for advanced colon neoplasms (not only cancer) of 70-78% and a specificity of 84% has been described *(Lieberman et al. 2001; Sung et al. 2003)*.

There are numerous studies published reporting compliance with sigmoidoscopy screening in the range of 23-81% *(Foley 1987; Cockburn et al. 1995; Rasmussen et al. 1999; Thiis-Evensen et al. 1999; Collett et al. 2000; Segnan et al. 2002; UK Flexible Sigmoidoscopy Screening Trial Investigators 2002; Gondal et al. 2003)*. In the larger Norwegian study, with 65% compliance, a drop in the participation rate with 4% occurred when combining the sigmoidoscopy with FOBT *(Gondal et al. 2003)*. We are keenly awaiting the results from four large RCTs on the efficacy in mortality reduction with sigmoidoscopy screening *(Palitz et al. 1997; UK Flexible Sigmoidoscopy Screening Trial Investigators 2002; Segnan et al. 2002; Gondal et al. 2003)*.

Participation in colorectal cancer screening

In colorectal cancer screening, the screening test could be a major determinant of the participation rate. As previously described, uptake of around 60-75% has been noted in fecal occult blood screening, but a much larger variation, between approximately 25% and 80%, has been demonstrated in the earlier sigmoidoscopy screening studies (see above). Most studies though, evaluating compliance with colorectal cancer screening, are not randomized in attempt to evaluate the compliance by different screening methods. One larger Italian randomized trial, comparing different screening strategies, demonstrated similar participation rates with FOBT and sigmoidoscopy (approximately 30%) *(Segnan et al. 2005)*. In a Swedish study comparing FOBT with sigmoidoscopy, the people invited to sigmoidoscopy also received a FOBT to make it possible to determine whether the person had a positive FOBT or not prior to possible extirpation of a neoplasm at sigmoidoscopy. This could of course have affected participation, but, in spite of this, the compliance was 59% and 49% for the FOBT- and the sigmoidoscopy-group, respectively *(Brevinge et al. 1997)*.

The participation in colorectal cancer screening trials is in general lower than the population-based programs of breast and cervical cancer screening (see below). As described earlier, with low participation, there will be a selection of people participating and a low effectiveness in terms of reducing mortality. Numerous studies have been published, trying to explain the factors associated with participation in colorectal cancer screening. Most studies have typically used interviews or self-administered question-

naires, but low response rates and lack of motivation, especially among people not participating, have limited the interpretation.

In the published studies of colorectal cancer screening participation, men have been more prone to participate than women *(Sutton et al. 2000; Weissfeld et al. 2002; Chao et al. 2004; Montano et al. 2004; Slattery et al. 2004; Turner et al. 2004; Denberg et al. 2005)*. Regarding ethnicity *(Weissfeld et al. 2002; Ioannou et al. 2003; Turner et al. 2004)* and marital status *(Vernon 1997)* the results have been inconsistent, but on the other hand there is a trend, as in the screening programs of breast and cervical cancer, of socio-economically disadvantaged people (low income and education) among the non-participants *(Neilson et al. 1995; Sutton et al. 2000; Wardle et al. 2000; McCaffery et al. 2002)*. Most studies also demonstrate that smoking is a predictor of non-participation *(Shapiro et al. 2001; Weissfeld et al. 2002; Chao et al. 2004; Slattery et al. 2004)*.

There is a congruent pattern of higher participation among people with a family history of colorectal cancer *(Chao et al. 2004; Slattery et al. 2004; Subramanian et al. 2004)*. Further, the participants in colorectal cancer screening have been shown to have a healthy lifestyle *(Larsen et al. 2006)* and an experience of good subjective health *(Sutton et al. 2000)*. Non-participants, on the other hand, have been demonstrated to have an "unhealthy" lifestyle *(Shapiro et al. 2001; Slattery et al. 2004)*. This could be an indication of self-selection to screening; people with good health and possibly lower cancer and mortality risks are participating and people with low socio-economic status and, speculatively, an "unhealthy" lifestyle with increased risks do not participate.

In general, awareness about colorectal cancer is low *(Wong et al. 2002; McCaffery et al. 2003; Keighley et al. 2004; Wee et al. 2005)*, but, even so, the non-participants may be less aware of colorectal cancer as a health problem and of the possible benefits of screening for the disease *(Seeff et al. 2004; Klabunde et al. 2006)*.

Participation in sigmoidoscopy screening

There are sigmoidoscopy screening studies where participants report experiencing low levels of pain *(Santavirta 2002; Segnan et al. 2002)* and embarrassment *(Cockburn et al. 1995; Segnan et al. 2002)*. Pain, discomfort and embarrassment has also been reported as relatively minor barriers among non-participants *(McCaffery et al. 2001)*, but fear of a positive finding is not *(Dent et al. 1983; Farrands et al. 1984; Neale et al. 1989)*. Absence of bowel symptoms and a low perceived susceptibility to bowel cancer are other factors associated with low interest in participation *(McCaffery et al. 2001)*.

There are few studies published regarding the quality of life after participation in sigmoidoscopy screening. Reassurance and relief among individuals with a negative test would be expected, as well as anxiety and distress among individuals with a positive test. False positive tests among participants in the PLCO Cancer Screening Trial (using sigmoidoscopy for colorectal cancer screening) had a negative impact on health related quality of life, but only in the short term *(Taylor et al. 2004)*. The adherence with the trial was poorer, though, among people with false positive tests, even if relief outweighed the negative emotions *(McGovern et al. 2004)*.

Overall, a majority of participants in sigmoidoscopy screening would participate again in the future *(Cockburn et al. 1995; Santavirta 2002)* and this opinion is important to communicate to others.

Economical aspects

The economical burden of CRC is high. The annual direct health care cost for a CRC patient undergoing surgery has been estimated to at least $10,000 the first three years following diagnosis *(Delco et al. 2005).* Theoretically, with the introduction of CRC screening, some of the costs of CRC treatment could be allocated to screening. Even if screening undoubtedly would reduce the incidence and mortality of CRC, questions remain as to which test to use, how frequently screening should be performed and at what ages to begin and end *(Pignone et al. 2002)*. As described earlier, to measure the cost-effectiveness of the different colorectal cancer screening test, one has to make assumptions about the effectiveness and adverse effects of each test and take into consideration the expected compliance. With an assumption of equal compliance; the more accurate tests (e.g. colonoscopy) are more cost-effective, particularly when compliance is assumed to be low *(Pignone et al. 2002)*.

For colonoscopy every 10 years, or the combination of annual FOBT and sigmoidoscopy every 5 years, the cost per life-year saved has been estimated to $10,000-25,000 *(Pignone et al. 2002)*. In the terms of cost per life year saved, sigmoidoscopy screening has been demonstrated as most efficient, followed by colonoscopy, biennial-, and annual FOBT *(O'Leary et al. 2004)*. Based on early data from the screening trial in Funen *(Kronborg et al. 1996)*, biennial FOBT screening in Sweden during a 10 year period directed at the group aged 45-75 years, would cost approximately 322,000 SEK to prevent one death, i.e. 100,000 SEK per life-year with three life-years saved per saved case and 65,000 SEK per life-year with five life-years saved (*Swedish Council on Technology Assessment in Health Care [SBU] 2001)*.

Despite the high mortality of colorectal cancer, it is important to remember that the lifetime risk of death from colorectal cancer is low for any individual in the community with no high-risk factors. More than 98% of the population is estimated not to benefit from screening to prevent death *(Thompson et al. 2006)*. Since only a small proportion of all deaths are due to colorectal cancer, the impact of colorectal cancer screening on all-cause mortality is low. This has to be considered when optimizing the economical resources of health care.

Cancer screening services in Sweden

In Sweden there are nationwide population based screening programs of the average-risk population for breast and cervical cancer. As for CRC screening, prostate cancer screening *(Sandblom et al. 2004; Sennfalt et al. 2004)* and lung cancer screening *(Swedish Council on Technology Assessment in Health Care 2002)* have been subjects for discussion.

Breast cancer screening

Since 1986, the Swedish National Board of Health and Welfare recommends screening mammography for all women 40-74 years old *(National Board of Health and Welfare 2002)*. The recommended screening interval is every 18 months for women younger than 55 years, otherwise biennial. Even if organized mammography screening service is running in Sweden, it has been subject to intense debate. The controversy is mainly concerning the effectiveness of mammography in reducing mortality, but also the potential harm of a false positive test.

Effectiveness

A recent published review of breast cancer screening with mammography by The Cochrane Collaboration, has estimated a mortality reduction of 20%, relative to no mammography screening, although 15% is believed more reasonable since the effect was lower in the highest quality trials *(Gotzsche et al. 2006)*. The ARR was 0.0005 or 0.05%, which means that 2000 women need to be *invited* to screening (NNS) to prevent one breast cancer death, but in addition there will be 10 healthy women with false positive tests treated unnecessarily.

Estimating the mortality reduction among women *actually being* screened, the results from the organized mammography screening service offered to Swedish women have been more promising. In an evaluation, covering an area where 45% of women targeted for screening live, the reduction in breast cancer mortality associated with screening, after adjustment for self-selection bias, has been estimated to 40-45% *(The Swedish Organised Service Screening Evaluation Group 2006a)*. The ARR was approximately 0.2%, generating a NNS of 500.

The cost per-life year saved in biennial breast cancer screening with mammography has been estimated to approximately $19,000 *(Leivo et al. 1999)*.

Participation

The participation rate in mammography screening is about 75% in Sweden *(The Swedish Organised Service Screening Evaluation Group 2006a)* and 70% in the U.S. *(Swan et al. 2003)*. Factors related to higher likelihood of participation are younger age, Caucasian race, high income, high education and living in urban areas *(Smith et al. 1992)*. Lower participation, though, has been shown with longer distance to the screening center *(Maxwell 2000; Bulliard et al. 2004)*. Moreover, married women are more frequent users of mammography, compared to never-married women (Smith *et al.* 1992). Regarding family history of breast cancer, some studies have shown a positive association *(Taplin et al. 1989; NCI Breast Cancer Screening Consortium 1990)*, but others have not *(Houts et al. 1991)*. Health care contact is another important factor associated with participation. Women with a regular physician or annual check-ups are about three times more likely to have had a mammography in the previous 12 months *(Smith et al. 1992)*. On the other hand, smoking women have lower mammography rates than non-smokers *(Rakowski et al. 2005)*. Among the non-participants, the two most common explanations for not having a mammography is that they are not aware that they needed a mammography, or their doctor had not told them to get one *(Smith et al. 1992)*. In a small Swedish questionnaire study of "definite non-participants" (never received and would not consider mammography), 11% claimed it was because of other medical problems *(Lidbrink et al. 1995)*.

To increase participation in population-based breast cancer screening, enhancement of breast cancer awareness in the population has been suggested *(Lagerlund et al. 2000)*. Another possibility to increase participation could be by modifying the invitation routines and, fortunately, most active recruitment strategies have been shown to be effective, e.g. a letter of invitation plus phone call, as compared with no intervention (Odds Ratio [OR] for participation was 2.53, 95% CI 2.02-3.18) *(Bonfill et al. 2001)*.

Cervical cancer screening

Organized screening for cervical cancer in Sweden was introduced in the mid-1960s *(Dillner 2000)*. All women 23-49 years old are invited to screening with Papanicolaou (Pap) smear every three years, and women 50-60 years old every five years. Close to 1

million tests are taken annually, although only approximately 30% are taken in the organized screening program *(Dillner 2000)*. The human papilloma virus (HPV) is important for the development of cervical cancer. HPV tests have a high sensitivity, but a low specificity, as compared to Pap smears *(Stenvall et al. 2007)*. HPV testing is a supplement in Pap smear screening and suggested as the follow-up test in women with a low-grade atypia *(Andersson et al. 2005)*.

Effectiveness

Randomized controlled trials evaluating the efficacy of cervical cancer screening were never performed in relation to introduction of the screening program in Sweden, but initial reports showed decreased incidence of invasive cervical carcinoma and mortality in areas subjected to screening *(Mahlck et al. 1994)*. Nevertheless, a 53% reduction in mortality has been estimated attributable to screening in Swedish material *(Mahlck et al. 1994)*.

The cost per life-year saved in triennial cervical cancer screening with Pap smear has been estimated to $4000 *(Duke University 1999)*.

Participation

The participation rate in organized cervical cancer screening varies greatly; from >85% in northern Sweden (Västerbotten) to 20-30% in southern Sweden (city of Malmö) *(Dillner 2000)*. In Malmö, though, 76% of eligible women had had a recent opportunistic test *(Dillner 2000)*. The factors affecting participation in cervical cancer screening, in general, follow the same pattern as for breast cancer screening; higher participation rates among younger women *(Maxwell et al. 2001)*, women with high income and education *(Segnan 1997)*, and low participation rates among ethnic minorities *(Seow et al. 2000)* and immigrants *(Harlan et al. 1991)*, single women *(Maxwell et al. 2001)*, and women living in rural areas *(Eaker et al. 2001a)*. Screening participants have been shown to have more frequent contact with their general practitioner *(Larsen et al. 1996)* or gynecologist *(Eaker et al. 2001a)* but, even though cervical cancer is associated with smoking *(Slattery et al. 1989; Levitz et al. 2004)*, it does not seem like smoking status can predict participation *(Orbell et al. 1995)*. There are few published studies of the impact of a family history of cervical cancer on participation in screening. This could be due to the fact that cervical cancer is a relatively rare cancer with, hence, relatively few affected families. According to the Swedish Cancer Register, the number of new cervical cancer cases reported in 2005 was 429, as compared to 6962 and 5665 breast- and colorectal cancer cases, respectively *(National Board of Health and Welfare 2007a)*.

As in mammography screening, there is a lack of awareness among the non-participants about the disease *(Eaker et al. 2001b)*. Information about the preventive effect of the screening test and the importance of taking the test with regular intervals, might increase participation *(Eaker et al. 2001b)*. Moreover, mail or phone reminders have been shown to increase cervical cancer screening participation significantly *(Eaker et al. 2004)*.

Colorectal cancer screening?

In Sweden, there has been one RCT with FOBT as the screening test. Only the preliminary results have been published *(Kewenter et al. 1994)*, but 15.5 years follow-up data, demonstrating a 16% reduction in colorectal cancer mortality *(Haglind et al. 2005)*, has been included in the referred review by The Cochrane Collaboration *(Hewitson et al. 2007)*. The Swedish National Board of Health and

Welfare is not recommending colorectal cancer screening due to lack of experiences of screening on the population level *(National Board of Health and Welfare 2007b)*. They have referred the issue to ”Research and Development” and are awaiting results from ongoing trials outside Sweden. In our neighboring country Finland, though, a carefully designed feasibility study to evaluate FOBT screening as a public health policy is now running *(Malila et al. 2005)*.

As opposed to screening with FOBT, the impact of sigmoidoscopy screening on colorectal cancer mortality reduction has not been evaluated. This must be evaluated in a randomized controlled trial (see above). Before considering a RCT in a Swedish setting, it is important to evaluate the feasibility of sigmoid-oscopy with regard to compliance, experiences among participants', technical aspects of the sigmoidoscopy, to identify potential non-participants and to estimate the effect of the possible selection of people participating. As described earlier, a high participation in screening is very important to be able to evaluate effectiveness and cost-effectiveness. If the feasibility study finds factors associated with non-participation, groups that would benefit from extra recruitment efforts could possibly be identified and special efforts could be made to target these groups to optimize participation.

AIMS

- To evaluate compliance with sigmoidoscopy screening for colorectal cancer among 60 year old Swedish men and women; to compare effects on uptake by two different invitation procedures; and to estimate the frequency of neoplasms among participants (paper I).

- To evaluate the participants' subjective experiences and the technical feasibility of screening sigmoidoscopies (paper II).

- Estimate the strength of associations between suspected risk factors for non-compliance and observed non-participation in sigmoidoscopy screening through multiple record linkages with demographic and health care registers (paper III).

- To compare non-participants' and participants' cancer incidence and mortality during follow-up for up to nine years after invitation to sigmoidoscopy screening and to estimate the relative rates in comparison with the matching general population (paper IV).

SUBJECTS AND METHODS

Why use sigmoidoscopy?

When designing the feasibility study of sigmoidoscopy screening underlying this thesis, two case-control studies had gained considerable attention; having had a sigmoidoscopy was associated with significantly decreased odds of colorectal cancer mortality (OR 0.21 [95% CI 0.08-0.52] *(Newcomb et al. 1992)* and OR 0.41 [95% CI 0.25-0.69] *(Selby et al. 1992)*), as compared to individuals who had never had one. In theory, sigmoidoscopy has potential as a screening tool since nearly two thirds of all colorectal cancer can be reached with the sigmoidoscope *(Atkin et al. 1993)*. Accordingly, Atkin *(1993)* proposed that one single sigmoidoscopy might be an effective screening strategy to identify risk groups between the age of 55 and 60.

Study population

In 1996, we randomly selected from the computerized population register, 2000 individuals born in 1935 or 1936 (59-61 years old) and living in the uptake areas of the University Hospital of Uppsala (in central Sweden) and the University Hospital of Lund (in southern Sweden). These two areas of Sweden were chosen because of their different incidence rates of colorectal cancer *(National Board of Health and Welfare 1996)*.

Study design and methods

The subjects were randomized into two different invitation methods (group 1 and 2). All subjects, regardless of allocation arm, received a written invitation, including a brief account of the descriptive epidemiology of colorectal cancer, a paragraph about the potential for reducing colorectal cancer mortality with screening, and a description of the aims and design of the study. A questionnaire was also included with questions concerning the subject's occupation, physical activity, diet, alcohol use, smoking, medical history including previous bowel examinations, and family history of cancer. The purpose of the enclosed questionnaire was to estimate risk factors for developing adenomas. Participants with adenomas (cases) were planned to be compared with the rest of the cohort of participants without adenomas (controls). The planned case-control study was unfortunately not viable due to the few cases generated (see below). After receipt of the mailed material, a nurse from the center telephoned the subjects assigned to group 1 to book an appointment for sigmoidoscopy. Up to ten attempts were made to reach each subject over the phone. If the invitee declined or did not answer, he/she was classified as a non-participant. Subjects with a secret phone number received a special second invitation by mail where they were asked to call the center themselves to make an appointment for sigmoidoscopy (43 subjects in Uppsala and 87 in Lund). In group 2, no active contact was made by the nurse; instead the invitees were asked to call the center themselves. If we did not hear from them within three weeks, a reminder was sent out. After a further three weeks, a second reminder was sent. If still no answer was received, or if the invitee responded in the negative, he/she was classified as a non-participant.

Paper I

All subjects scheduled for a sigmoidoscopy received a written confirmation by mail together with an oral bowel preparation kit (PicoSalax™) and a rectal enema (Toilax™). Moreover, enclosed were two test tubes to be used if the subject agreed to donate a fecal sample. The last three days before the sigmoidoscopy the participants

were recommended to eat a low fiber diet and after breakfast on the day before the examination they were asked to drink only broth and clear drinks.

All sigmoidoscopies were performed by surgeons (11 in Uppsala and 4 in Lund) on an outpatient basis. No biopsies were performed, instead all subjects with a suspected cancer or adenoma, but also >3 hyperplastic polyps *(Cappell et al. 1989; Kellokumpu et al. 1991)*, were rescheduled for a complete colonoscopy. At colonoscopy all observed lesions were either removed (polyps) or biopsed for pathological anatomical diagnosis (PAD – other lesions including cancers). The PAD result determined subsequent management, i.e. surgery, surveillance or no surveillance. Polyps with both hyperplastic and adenomatous features were classified according to the dominantly histology.

Paper II

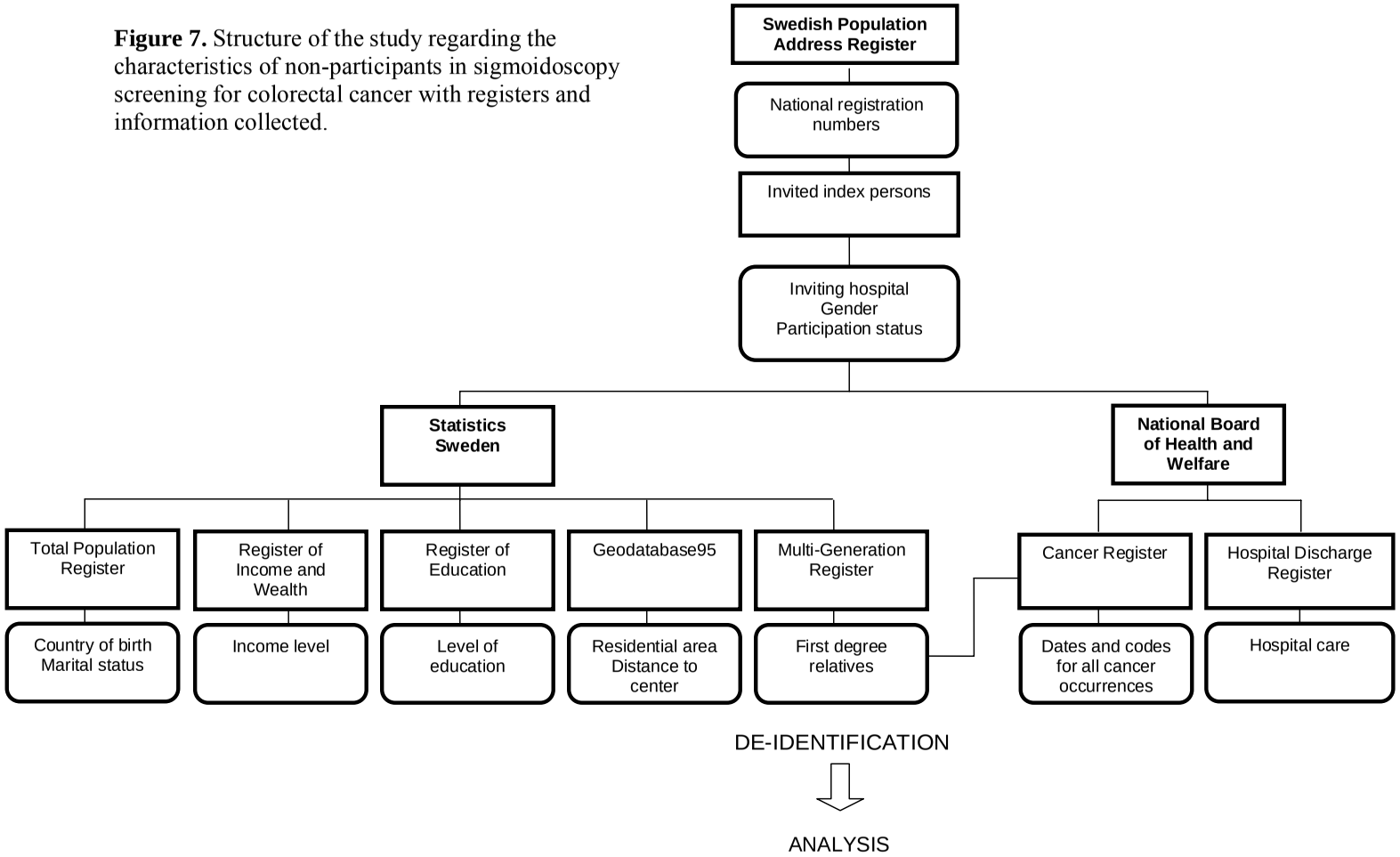
After the sigmoidoscopies at the Uppsala center, the participants anonymously filled out a 20-item questionnaire in a separate room. A nurse was nearby to assist in case of difficulties. The questions concerned the experiences of the invitation, bowel preparation and the actual examination. There were also questions about time off work and if the participant would recommend screening sigmoidoscopy to a friend. Twelve of the questions had graded responses on a 10 cm horizontal visual analog scale (VAS) and eight (about nominal scale variables) were answered by check boxes. There was also space for open-ended comments.

The endoscopists also filled out a protocol for each patient documenting the macroscopic findings and the anatomical level reached with the endoscope. In the absence of a level assessment, we used the nurse's report of how many centimeters the instrument had passed anus and assumed that the descending colon was reached at 50 centimeters. The nurse also recorded the time required for the sigmoidoscopy. The endoscopist estimated the subjects' discomfort on a VAS scale (similar to that one used in the participants' questionnaire) and the bowel preparation as good, acceptable or inadequate. In case of an incomplete examination the reasons were noted.

Paper III

The design of this study regarding the characteristics of non-participants is illustrated in Figure 7. A computer file with the invitees' national registration numbers together with information about inviting center (Uppsala, Lund), gender and participation status was sent to Statistics Sweden. There, data on country of birth (Sweden, other Nordic countries, Europe except Nordic countries, or outside Europe) and marital status were obtained from the Total Population Register *(Statistics Sweden 2002)*. Income data was collected from the Register of Income and Wealth *(Statistics Sweden 2006a)* and information on level of education was taken from the Register of Education *(Statistics Sweden 2004a)*. The Geodatabase95 provided information on the individual's area of residence and was also used to calculate the distance to the screening center (see below). Further, the national registration numbers of all parents, siblings and children of the invitees were obtained from the Multi-Generation Register *(Statistics Sweden 2004b)*. The Cancer Register provided us with dates and diagnostic codes for cancer occurrences in the invitees and their first degree relatives *(National Board of Health and Welfare 2006)*. Moreover, we collected information on hospital care during the preceding 5 years among invitees from the Hospital Discharge Register *(National Board of Health and Welfare 2005a)*.

Figure 7. Structure of the study regarding the characteristics of non-participants in sigmoidoscopy screening for colorectal cancer with registers and information collected.



Paper IV

At the Cancer Register *(National Board of Health and Welfare 2006)*, we obtained information on all occurrences of cancer after the invitation classified according to the International Classification of Diseases 7th revision (ICD-7). We grouped neoplastic outcomes into total cancer (ICD-7: 140-209), colorectal cancer (ICD-7: 153, 154), other gastrointestinal cancer (ICD-7: 150-152, 155-159), lung cancer (ICD-7: 162, 163), and smoking-related cancers (ICD-7: 140-148, 150-151, 157, 161-162, 171, 180-181) *(Levitz et al. 2004)*.

Dates and causes of death, classified according to ICD-10, were obtained from the Causes of Death Register *(National Board of Health and Welfare 2005b)*; all-cause mortality, mortality from all neoplastic diseases (ICD-10: C00-D48), gastrointestinal cancer specifically (ICD-10: C15-C26, C48), as well as mortality from diseases of the circulatory system (ICD-10: I00-I99). We also studied accident- (ICD-10: V01-Y98), alcohol- and drug-related mortality (ICD-10: F10-F19). Since the register lacked information about the causes of deaths that had occurred after 2003-12-31, follow-up for specific causes of deaths was terminated two years earlier than the follow-up for all-cause mortality (see below).

To ensure correct censoring, we also requested information from Statistics Sweden about the dates of emigration for cohort members who left Sweden during follow-up.

Statistical methods

We used the χ^2 test in paper I to compare proportions of participants between the two invitation groups, screening centers and gender.

In paper II we used descriptive statistics including medians and ranges based on VAS data concerning the participants' experiences of the sigmoidoscopy and the non-parametric Mann-Whitney U-test to assess differences between the invitation groups. We also estimated the relative risk (RR) with 95% confidence intervals (CI) to report pain exceeding >66 mm on the VAS scale. To analyze determinants of self-reported discomfort, pain and sensation of distension among the participants, we used multivariable linear regression models. We also used multivariable linear regression to analyze determinants of participants' discomfort estimated by the endoscopist, while adjusting for the endoscopists' different frames of reference. In the models, statistical significance of the individual coefficients was estimated with t-tests (p-value of <0.05).

In paper III we performed logistic regression to model odds ratios (ORs) with 95% CIs for associations of non-participation with the different background factors of interest, with and without adjustment for other co-factors. Continuous variables (distance, income, number of days in hospital in the preceding 5 years, and number of inhabitants in the area of residence) were categorized prior to any analysis of the effect. We also tested the trend for continuous variables through a logistic regression model in which the odds for non-participation was the dependent variable. The explanatory variable was the continuous variable of interest and all other variables were included for adjustment. We performed analysis of all invitees (combined), but we also stratified by screening center (not shown). Moreover, we compared our results (ORs) with the RRs obtained with log-link binomial regression in GLIM *(Wacholder 1986)*.

Follow-up in paper IV began at the date of invitation, i.e. May 1996 in Uppsala and November 1996 in Lund. Censoring occurred at the date of death, emigration, or end of the follow-up (2004-12-31 for various cancer incidences, 2003-12-31 for

various cause-specific mortalities and 2005-12-31 for all-cause mortality) whichever occurred first. To compare participants *vs.* non-participants with regard to cancer incidence and mortality, a Poisson regression model was used, adjusting for gender, yielding estimates of incidence rate ratio (IRR) and mortality rate ratio (MRR). The observed number of incident cases was also compared with the expected number based on the incidence in the matching general population. The expected number was calculated by multiplying the observed number of person-years at risk in the studied cohorts in 5-year age group, gender and calendar year strata, by the corresponding stratum-specific incidence rates in the general population. The resulting measure, the standardized incidence ratio (SIR) and correspondingly the standardized mortality ratio (SMR), can be interpreted as the RR with the matching general population as reference. We computed 95% CIs with the assumption that the observed number of events followed a Poisson distribution.

Data sources

Infodata

Swedish Population Address Register (SPAR) is a register of name, date of birth and addresses of all people nationally registered in Sweden *(Infodata 2007)*. Infodata AB administrates the register commissioned by the Government. Our original random selection was made from this register.

Statistics Sweden

Total Population Register started in 1968 and is an extended demographic register of the residents of Sweden and includes, e.g., information on country of birth and marital status. It is most often used to provide background information about people included in different research projects. The register also provided us with information on movements within Sweden prior to invitation and the dates on emigration (and immigration) for cohort members who left Sweden during follow-up *(Statistics Sweden 2002)*.

Register of Income and Wealth is based on the tax returns submitted to the National Tax Board of Sweden *(Statistics Sweden 2006a)*.

Register of Education started in 1984 and is annually updated with the highest degree of education of all individuals in Sweden between 15 and 74 years of age *(Statistics Sweden 2004a)*.

Geodatabase95 is a database with information on all domiciles in Sweden by the end of 1995. Hereby, we could obtain exact location of the place of residence and the character of the residential area of the invitees *(Statistics Sweden 2006b)*. Further, since all domiciles have a map coordinate, we could use the coordinate in a GIS (Geographic Information System) program to calculate the distance to the screening center.

Multi-Generation Register links all Swedish individuals born from 1932 onwards to their parents (biological or adoptive) and, thus, also to their siblings *(Statistics Sweden 2004b)*. It has about 65% coverage on mothers and fathers of people born in 1935 and 36 *(Bruhn 2004)*.

The Swedish National Board of Health and Welfare

Hospital Discharge Register covers Uppsala since 1964 and Lund since 1970, but became nationwide first in 1987. The register comprises information on admission and discharge dates, total days spent in hospital, and up to eight diagnoses at discharge. Under-reporting in the Hospital Discharge Register has been estimated to about 2% *(National Board of Health and Welfare 2005a)*.

Cancer Register has operated since 1958 and provides dates and diagnostic codes according to the 7th revision of the International Classification of Diseases (ICD-7) for all cancer occurrences in Sweden. Approximately 99% of all cancers are cytologically or histologically verified. The register does not include information obtained from death certificates only *(National Board of Health and Welfare 2006)*.

Cause of Death Register comprises all deaths of Swedish residents (citizens or not) and irrespective of whether the deaths occurred in Sweden or not. The information is taken from the death certificates, which is missing for <1% of deaths included in the register *(National Board of Health and Welfare 2005b)*. Date of death, underlying cause of death (the disease that initiated the chain of diseases that finally resulted in death), multiple causes of death, and whether autopsied or not are some variables included in the register. Only 14% of death certificates were based on autopsies in 2003 *(National Board of Health and Welfare 2005b)*. The causes of death are classified according to 10th revision of the International Classification of Diseases (ICD-10).

RESULTS

Participation and findings (paper I)

Thirty-nine per cent (770/1988) of all invited individuals participated, 47% (469/995) in Uppsala and 30% (301/993) in Lund ($p<0.01$) (Table 5). There were no significant differences in participation by the randomly assigned invitation groups (contact made by a nurse or the invitee) or gender. In the group from Uppsala who were asked to call themselves, 50% participated after the invitation, 36% after the first reminder and 14% after the second.

Table 5. Participation by center and invitation group among 1988 subjects* 59-61 years old invited to sigmoidoscopy screening

	Invited			No. of participants (%)		
	Total	Men	Women	Total	Men	Women
Uppsala (total)	995	501	494	469 (47)	225 (45)	244 (49)
Group 1†	501	255	246	248 (50)	118 (46)	130 (53)
Group 2‡	494	246	248	221 (45)	107 (43)	114 (46)
Lund (total)§	993	509	484	301 (30)	161 (32)	140 (29)
Group 1†	502	249	253	155 (31)	85 (34)	70 (28)
Group 2‡	491	260	231	146 (30)	76 (29)	70 (30)

* 12 subjects, out of 2000 randomly selected, were not invited because they had moved out of the study area.
† Called up by nurse.
‡ Asked to call themselves.
§ In the published paper I the center is denoted Malmö/Lund due to a temporarily merge of the two hospitals.

In total, 11% of the participants had polyps that were deemed to be adenomatous, with a significant gender difference only at the Uppsala center (13% [29/225] and 6% [14/244] of men and women, respectively, $p<0.01$). There was a difference in polyp prevalence by center (9% [43/469] and 14% [42/301] in Uppsala and Lund, respectively, $p=0.04$).

According to our study protocol, subjects with a suspected cancer, adenoma or >3 hyperplastic polyps were to be rescheduled for a follow-up colonoscopy. In total 98 (13%) of participants were rescheduled for a follow-up colonoscopy; 85 (11%) with an "adenoma", one (0.1%) with >3 hyperplastic polyps and 12 (1.6%) because of other findings (11 hyperplastic polyps and one suspected inflammatory bowel disease). No suspected cancers were found at sigmoidoscopy. However, one woman had a stricture that could not be bypassed by the sigmoidoscope. A DCBE showed a suspected tumor and she was planned for surgery that turned out to be negative.

At colonoscopy, three invasive and two *in situ* adenocarcinomas were diagnosed, all within the reach of the sigmoidoscope (15-30 cm from anus). Fifty-five true adenomas were found in 46 subjects (12 women). Twelve subjects had adenomas ≥1cm within the reach of the sigmoidoscope (60 cm) and six subjects had proximal adenomas.

Participants' experience (paper II)

Among the 469 participants in Uppsala, all but one filled out the questionnaire after the examination (some questions had blank answers though). Ninety-eight per cent of the subjects thought that the invitation letter adequately described the procedure. Twelve per cent took half a day or more off work for the preparations and 39% took half a day or more off work for the sigmoidoscopy.

Overall, the participants' answers to the questions about self-perceived unrest or discomfort were skewed towards low values on the VAS scale (Figure 8). Except for the sensations of pain and distension, more than half of the participants placed their mark in the lowest fourth of the VAS scale for all dimensions that we inquired about. However, not all participants experienced the sigmoidoscopy as innocuous. Ratings for pain and sensation of distension in the upper half of the VAS scale were noted in approximately 20% and 30% of participants, respectively.

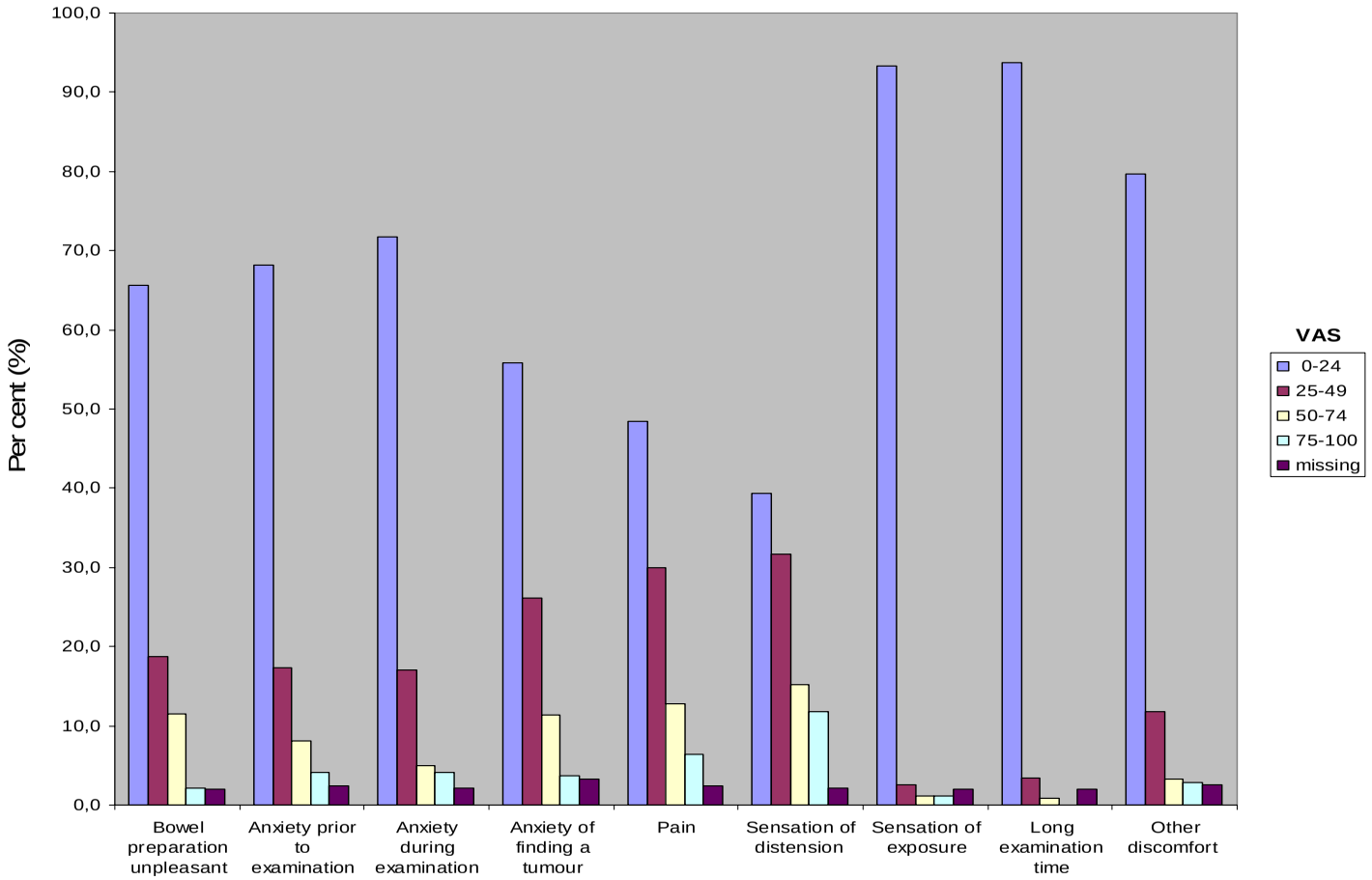
There were no significant differences between the two invitation groups with respect to the proportion with ratings >66 mm on the VAS scale. However, although the numerical difference was slight (median 7 mm *vs.* median 5 mm), the self-rating of "other discomfort", was significantly higher in the group with subjects who were asked to call for an appointment themselves, as compared to the group that was called up by the nurse (i.e. participants in that group had higher VAS scores and, thus, higher rank-sum value).

There were significant positive associations of pain and other discomfort during the sigmoidoscopy with appre-hension of long examination time and anxiety *during* the examination. On the other hand, anxiety *prior* to the sigmoidoscopy showed a significant negative association with pain. Sensation of bowel distension and apprehension of long examination time had highest impact on pain during the sigmoidoscopy and an uncomfortable bowel preparation ex-plained some of the "other discomfort". However, the impact of each determinant was quantitatively small.

All but six subjects indicated that they were willing to undergo another sigmoidoscopy within 2-10 years, if screening reduced the risk of colorectal cancer mortality, and approximately 80% would recommend a friend to participate.

The examiner-rated VAS values of the participants' discomfort differed among the endoscopists with median VAS ratings ranging between 10 and 29 mm. Across all examiners, the values were most strongly linked to gender of the patient (with low scores for men), intubation level (with less discomfort with increasing depth), and duration (increased discomfort with longer time). The discomfort among subjects with a positive finding was not rated differently from subjects with no finding (median 18 mm [range 1-89 mm] *vs.* median 16 mm [range 1-83 mm], p=0.37).

Figure 8. The screening participants' experience of the sigmoidoscopy examination as indicated on VAS scales (0-100 mm).



Technical feasibility (paper II)

The mean intubation depth was 59 cm (95% CI 58.4-59.2, range 28-60) and the mean examination time was 5.8 minutes (95% CI 5.6-6.1, range 2-23). In both men and women, 80% of the sigmoidoscopies were estimated to reach the descending colon. Twenty sigmoidoscopies (4%) were incomplete (14 women, 6 men). At least eleven of these failures were partly due to pain. Two examinations were incomplete due to unclean bowel only. The bowel preparation was good or acceptable in 98% of participants.

Characteristics of invitees associated with non-participation (paper III)

As compared with paper I, with no significant difference in participation between men and women, male gender was associated with significantly increased odds of non-participation when adjusting for confounding factors (OR=1.27, 95% CI 1.03-1.57, relative to female) (Table 6). Being unmarried or divorced (OR=1.69, 95% CI 1.23-2.30, and OR=1.49, 95% CI 1.14-1.95, respectively, relative to married) and having an income in the lowest tertile (OR=1.68, 95% CI 1.27-2.23, $p_{trend}<0.01$, relative to the highest) was also associated with non-participation. Having <9 years of education was less clearly linked to non-participation (OR=1.21, 95% CI 0.92-1.59, relative to university). Residents of communities with <10,000 inhabitants showed an almost 30% lower risk of non-participation, as compared to residents of bigger towns (≥10,000 inhabitants) ($p_{trend}=0.05$). There was low non-participation among individuals who had a first degree relative with a documented history of colorectal cancer (OR=0.65, 95% CI 0.43-0.97, relative to no history). The latter was the only finding of the above that was not significant also in the log-link binomial regression model.

Hospital stay >10 days in the 5 years preceding the invitations was weakly associated with non-participation (OR=1.25, 95% CI 0.92-1.72, $p_{trend}=0.02$, relative to 0-3 days). Neither longer distance to the screening center nor immigrant status seemed to be linked to non-participation.

Table 6. Uni- and multivariable logistic regression analyses of associations between background factors and non-participation, measured as odds ratios (ORs) with 95% confidence intervals (CIs), in 1986 Swedish residents 59-61 years old invited to sigmoidoscopy screening

Background factor	Frequency Non-participants/ Study group	Unadjusted OR (95% CI)	Minimally-adjusted* OR (95% CI)	Fully-adjusted† OR (95% CI)
Inviting hospital				
Lund (southern)	689/992 (69%)	1.00	1.00	1.00
Uppsala (central)	526/994 (53%)	0.49 (0.41-0.59)	0.48 (0.39-0.59)	0.41 (0.33-0.52)
Invitation procedure				
Asked to call	617/985 (63%)	1.00	1.00	1.00
Called up by nurse	598/1001 (60%)	0.89 (0.74-1.06)	0.90 (0.73-1.10)	0.89 (0.74-1.08)
Gender				
Female	599/985 (61%)	1.00	1.00	1.00
Male	616/1001 (62%)	1.03 (0.86-1.24)	1.20 (0.96-1.51)	1.27 (1.03-1.57)
Country of birth				
Sweden	1058/1737 (61%)	1.00	-	1.00
Elsewhere	157/249 (63%)	1.10 (0.83-1.44)	-	0.87 (0.64-1.18)
Marital status				
Married	818/1412 (58%)	1.00	-	1.00
Unmarried	181/252 (72%)	1.85 (1.38-2.48)	-	1.69 (1.23-2.30)
Divorced	216/322 (67%)	1.48 (1.15-1.91)	-	1.49 (1.14-1.95)
Income level				
Highest tertile	347/618 (56%)	1.00	1.00	1.00
Middle tertile	427/698 (61%)	1.23 (0.99-1.53)	1.33 (1.03-1.72)	1.28 (1.01-1.64)
Lowest tertile	441/670 (66%)	1.50 (1.20-1.88)	1.75 (1.32-2.32)	1.68 (1.27-2.23)
Education‡				
University	281/480 (59%)	1.00	-	1.00
≥ 9 years but not university	454/784 (58%)	0.97 (0.77-1.23)	-	0.90 (0.70-1.16)
< 9 years	461/701 (66%)	1.36 (1.07-1.73)	-	1.21 (0.92-1.59)

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Residential area				
Town[§]	617/957 (64%)	1.00	-	1.00
Small town[‖]	397/665 (60%)	0.82 (0.67-1.00)	-	0.72 (0.54-0.96)
Village/rural[¶]	201/364 (55%)	0.68 (0.53-0.87)	-	0.72 (0.53-0.99)
Distance to screening center				
<5 km	433/671 (65%)	1.00	-	1.00
5 to 14.9 km	469/742 (63%)	0.94 (0.76-1.17)	-	0.87 (0.64-1.19)
15 km or longer	313/573 (55%)	0.66 (0.53-0.83)	-	1.03 (0.74-1.43)
A previous history of cancer				
No	1136/1864 (61%)	1.00	-	1.00
Yes	79/122 (65%)	1.18 (0.80-1.73)	-	1.08 (0.72-1.63)
Family history of colorectal cancer				
No	1159/1878 (62%)	1.00	-	1.00
Yes	56/108 (52%)	0.67 (0.45-0.99)	-	0.65 (0.43-0.97)
Family history of any cancer excluding colorectal				
No	730/1182 (62%)	1.00	-	1.00
Yes	485/803 (60%)	0.94 (0.78-1.13)	-	0.97 (0.80-1.18)
Hospital stay five years preceding invitation				
0-3 days	925/1530 (60%)	1.00	-	1.00
4-10 days	133/223 (60%)	0.97 (0.73-1.29)	-	1.02 (0.76-1.38)
>10 days	157/233 (67%)	1.35 (1.01-1.81)	-	1.25 (0.92-1.72)

[*] Adjusted for center, invitation procedure, gender, and income level.
[†] Adjusted for center, invitation procedure, gender, country of birth, marital status, income level, education, residential area, distance to screening center, previous history of cancer, family history of colorectal- and any other cancer, and hospital stay five years preceding invitation.
[‡] Two participants and 19 non-participants had missing data on educational level. They were assigned a separate term and were thus retained in the model, but the parameter estimates are not shown in the table.
[§] 10,000 inhabitants or more.
[‖] 1,000 to 9,999 inhabitants.
[¶] <1,000 inhabitants.

Cancer incidence and mortality after nine years follow-up (paper IV)

Cancer incidence

Participants and non-participants did not differ with regard to overall cancer incidence, but non-significantly higher incidence rates were noted among non-participants for colorectal cancer IRR=2.2 (95% CI 0.8-5.9), other gastrointestinal cancer IRR=2.7 (95% CI 0.6-12.8), lung cancer IRR=2.2 (95% CI 0.8-5.9), and smoking-related cancer IRR=1.4 (95% CI 0.7-2.5) (Table 7).

Table 7. Cancer incidence (per 1000 person-years) among 1215 non-participants relative to 771 participants in screening sigmoidoscopy. Relative risks are expressed as gender-adjusted incidence rate ratios (IRR) with 95% confidence intervals (CI).

Outcome (ICD-7)*	**Non-participants**		**Participants**		**IRR‡ (95% CI)§**
	Observed	Incidence†	Observed	Incidence†	
All-site cancer (140-209)	115	13.4	75	13.1	1.02 (0.8-1.4)
Colorectal cancer (153, 154)	16	1.7	5	0.8	2.2 (0.8-5.9)
Other gastro-intestinal cancer (150-152, 155-159)	8	0.9	2	0.3	2.7 (0.6-12.8)
Lung cancer (162, 163)	16	1.7	5	0.8	2.2 (0.8-5.9)
Smoking-related cancer‖	32	3.5	16	2.6	1.4 (0.7-2.5)

* International Classification of Diseases 7th revision.
† Incidence rate per 1000 person-years.
‡ IRR=Gender-adjusted incidence rate ratio.
§ 95% CI=95% confidence interval.
‖ ICD-7: 140-148, 150-151, 157, 161-162, 171, 180-181.

Notably, during the 16 month screening period, three of five colorectal cancers were diagnosed among the participants, as compared to one of 16 among the non-participants.

Relative to the matching general population, the risk of the selected cancers studied tended to be increased among non-participants (SIR >1.0) and decreased among participants (SIR <1.0) (Table 8).

Table 8. Standardized incidence ratios (SIR) with 95% confidence intervals (CI) for all-site and selected cancers among 1215 non-participants and 771 participants in sigmoidoscopy screening. For observed number of cancers, please refer to Table 7.

Outcome (ICD-7)*	**Non-participants**		**Participants**	
	Expected	SIR† (95% CI)‡	Expected	SIR† (95% CI)‡
All-site cancer (140-209)	108.3	1.1 (0.9-1.3)	72.3	1.0 (0.8-1.3)
Colorectal cancer (153, 154)	12.7	1.3 (0.7-2.1)	8.6	0.6 (0.2-1.4)
Other gastro-intestinal cancer (150-152, 155-159)	8.5	0.9 (0.4-1.9)	5.8	0.3 (0.0-1.3)
Lung cancer (162, 163)	10.0	1.6 (0.9-2.6)	6.8	0.7 (0.2-1.7)
Smoking-related cancer§	26.9	1.2 (0.8-1.7)	18.3	0.9 (0.5-1.4)

* International Classification of Diseases 7th revision.
† SIR=Standardized Incidence Ratio, i.e., incidence relative to the age-, gender- and calendar period-matched Swedish population.
‡ 95% CI=95% confidence interval.
§ ICD-7: 140-148, 150-151, 157, 161-162, 171, 180-181.

Mortality

Overall, mortality was statistically significantly higher among non-participants relative to participants (Table 9): all-cause mortality (MRR=2.4, 95% CI 1.7-3.4), total cancer mortality (MRR=1.9, 95% CI 1.1-3.5), gastrointestinal cancer mortality (MRR=4.7, 95% CI 1.1-20.7) and mortality from circulatory diseases (MRR=2.3, 95% CI 1.2-4.2). After excluding the invitees with cancer diagnosed within 5 years prior to invitation, the excess cancer mortality among non-participants remained; MRR for total cancer was 2.5 (95% CI 1.8-3.6) and for gastrointestinal cancer 4.3 (95% CI 0.97-19.1).

Table 9. Mortality (per 1000 person-years) among 1215 non-participants relative to 771 participants in screening sigmoidoscopy. Relative risks are expressed as gender-adjusted mortality rate ratios (MRR) with 95% confidence intervals (CI).

Cause of death (ICD-10)*	**Non-participants**		**Participants**		**MRR‡ (95% CI)§**
	Observed	Mortality†	Observed	Mortality†	
All-cause	151	14.6	42	6.0	2.4 (1.7-3.4)
Neoplastic diseases (C00-D48)	43	5.2	15	2.7	1.9 (1.1-3.5)
Gastrointestinal cancer (C15-C26, C48)	14	1.7	2	0.4	4.7 (1.1-20.7)
Circulatory diseases (I00-I99)	44	5.3	13	2.3	2.3 (1.2-4.2)
Accident-, alcohol- and drug-related deaths‖	5	0.6	2	0.4	1.7 (0.3-8.6)

* International Classification of Diseases 10th revision.
† Mortality rate per 1000 person-years.
‡ MRR=Gender-adjusted mortality rate ratio.
§ 95% CI=95% confidence interval.
‖ ICD10: V01-Y98, F10-F19.

Relative to the matching general population, there was a trend among non-participants suggestive of an increased mortality risk (Table 10): from all causes (SMR=1.2 [95% CI 0.99-1.5]), from gastrointestinal cancer (including colo-rectal cancer) (SMR=3.1 [95% CI 1.7-5.3]), and from circulatory diseases (SMR=1.4 [95% CI 0.99-1.8]). Among the participants, there was a statistically significantly decreased risk by 50% (SMR=0.5 [95% CI 0.3-0.7]) for all-cause mortality, and by 40% for mortality from cancer (SMR=0.6 [95% CI 0.3-0.97]), and by a non-significant 40% for mortality from circulatory diseases (SMR=0.6 [95% CI 0.3-1.02]), relative to the matching general population (Table 10).

Table 10. Standardized mortality ratios (SMR) with 95% confidence intervals (CI) for all-cause and selected cause-specific deaths among 1215 non-participants and 771 participants in sigmoidoscopy screening. For observed number of deaths, please refer to Table 9.

Cause of death (ICD-10)*	**Non-participants**		**Participants**	
	Expected	SMR† (95% CI)‡	Expected	SMR† (95% CI)‡
All-cause	91.7§	1.2 (0.99-1.5)	61.7§	0.5 (0.3-0.7)
Neoplastic diseases (C00-D48)	37.9	1.1 (0.8-1.5)	25.5	0.6 (0.3-0.97)
Gastrointestinal cancer (C15-C26, C48)	4.5	3.1 (1.7-5.3)	3.0	0.7 (0.1-2.4)
Circulatory diseases (I00-I99)	32.3	1.4 (0.99-1.8)	21.7	0.6 (0.3-1.02)
Accident-, alcohol- and drug-related deaths‖	5.4	0.9 (0.3-2.2)	3.6	0.6 (0.1-2.0)

* International Classification of Diseases 10th revision.
† SMR=Standardized Mortality Ratio, i.e., mortality relative to the age-, gender- and calendar period-matched Swedish population.
‡ 95% CI=95% confidence interval.
§ Since follow-up for all-cause mortality in Table 9 was two years longer than in this table (see methods section), the observed number of deaths cannot be derived from Table 9. The observed numbers were 110 and 31 among non-participants and participants, respectively.
‖ ICD10: V01-Y98, F10-F19.

Even though we did not intend to explain the morbidity and mortality differences through adjustments for the different background factors, we investigated how factors related to socio-economic status (marital status, income and education) were distributed among subjects who died during follow-up and among those who survived (Table 11). Overall, these distributions differed markedly. The divorced subjects, those with the lowest tertile of income, and those <9 years of education were over-represented in the group who died.

Table 11. Frequency distribution after nine years follow-up by marital status, income level and education among 1941 subjects[*] invited to sigmoidoscopy screening

Background factor	**No. living (n=1748) (%)**	**No. dead by any cause (n=193) (%)[†]**	**P-value[‡]**
Marital status			
Married	1270 (73%)	108 (56%)	<0.01
Unmarried	210 (12%)	39 (20%)	<0.01
Divorced	268 (15%)	46 (24%)	<0.01
Income level			
Highest tertile	553 (32%)	47 (24%)	0.08
Middle tertile	619 (35%)	66 (34%)	0.74
Lowest tertile	576 (33%)	80 (41%)	0.02
Education[†]			
University	434 (25%)	24 (12%)	<0.01
≥ 9 years but not university	698 (40%)	76 (39%)	0.88
< 9 years	599 (34%)	91 (47%)	<0.01
Missing data on education	17 (1%)	2 (1%)	0.93

[*] 45 subjects censored.
[†] The sum could deviate from 100 due to rounding.
[‡] Estimated with χ^2 test

GENERAL DISCUSSON

Methodological considerations

Study design

Our study is a population based cohort study of subjects whose exposure was the invitation to take part in sigmoidoscopy screening or the actual participation. The study population is the 2000 invitees randomly selected from the population register and the source population is all 59-61 year old people living in the uptake areas of the University Hospitals of Uppsala and Lund. A schematic figure of the study design and a table of the different exposures and outcomes measured by paper are illustrated below (Figure 9 and Table 12).

Figure 9. The design of the cohort study of 2000 randomly selected 59-61 year old subjects invited to sigmoidoscopy screening for colorectal cancer.

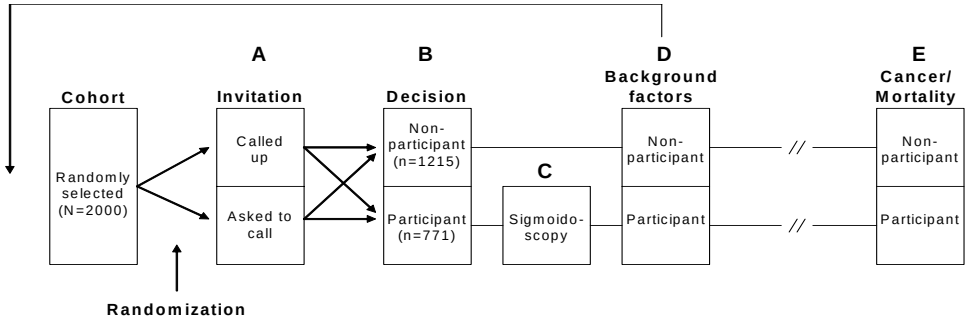

Table 12. The different exposures and outcomes measured in the cohort study of sigmoidoscopy screening by paper. Capital letters refer to Figure 9.

	Exposure	**Outcome**
Paper I (A+B+C)	Two different invitation methods	Participation or non-participation Diagnostic outcome (findings)
Paper II (A+C)	Two different invitation methods Personal traits (e.g. anxiety)	Subjective experience of the examination Pain and discomfort
Paper III (A*+B+D)	Background factors	Participation or non-participation
Paper IV (B+E)	Participation or non-participation	Cancer incidence and mortality

* Invitation method (called up by nurse or asked to call themselves) included in analysis.

In paper I we have demonstrated the frequencies of participants and non-participants by invitation method, gender, center and the findings at sigmoidoscopy among participants.

In paper II we evaluated the possible differences in the experience of the sigmoidoscopies between the different invitation methods and analyzed determinants of pain and discomfort (e.g. anxiety before the examination).

In paper III we used nested case-control approach to investigate the independent associations of background factors with participation. The strength of study III is that we have used register based information instead of interviews or questionnaires. Not only could we use information from *all* invited ("100% response rate"), but also, the information collected is less likely to be affected by bias (see below). One has to keep in mind, that the OR generated faithfully represents RR if the outcome is rare, and if not the deviation increases with effect size. OR=1.69 for non-participation among unmarried, as compared to married, is not the same as a 69% increased risk. With the same data, odds ratio gives a stronger picture of the association than the estimated relative risk (with OR below 1.0 the RR is higher and with OR above 1.0 the RR is lower), and the larger the effect size, the larger the difference. We therefore compared our results with the RRs obtained with log-link binomial regression, but did not find any larger differences of our results (see above).

In paper IV the outcomes measured are cancer incidence and mortality during the follow-up period for up to nine years. One has to keep in mind that our pretension in paper IV is not to evaluate the efficacy of sigmoidoscopy screening in reducing colorectal cancer mortality or possible decreased incidence in the long term perspective. In the short term, the cancer incidence is expected to increase among participants due to the finding of early stages of the disease (not yet clinically presented). Regarding the colorectal cancer mortality, the removal of adenomas is not expected to decrease mortality in such a short time and the few cancers found during the screening period (three cases) could scarcely have had any major impact. Instead, there is a strong element of self-selection which is the most likely reason for our results.

Validity

Uncontrolled selection as a threat to the external validity

Selection of suitable subjects to a study meant to generate knowledge to others than the individuals under study, i.e., knowledge that can be generalized to broad categories of humans, is not only a matter of how well the study subjects are representative of the target population in a narrow statistical sense *(Rothman et al. 1998)*. Nonetheless, the representative random sample of 59-61 year-old individuals in two hospital uptake areas, made possible through the high-quality and continuously updated computerized population registers in Sweden, emulating the population that will likely be targeted in a full-scale screening program, must be seen as a strength of our study. Also, the access to register-based background information about all invitees, regardless of whether they participated or not, is an unusual element of our study. This virtually eliminates selection bias due to non-response/non-participation, common in most studies that are dependent on the active involvement of the studied subjects. The evaluation of the diagnostic outcome and subjective experience of the examination, on the other hand, was based on the self-selected proportion that actually participated in the study and underwent the screening sigmoidoscopy. If the self-selection forces in the study would be

identical to those in operation in a real-life screening program, the subjects screened within the study would likely be representative of individuals participating in routine screening. However, the results of the analysis in paper III suggests that the participation rate may vary considerably between centers above and beyond the variation that is explained by suspected risk factors for non-participation. Also, the fact that all invitees were informed that the invitation was part of a scientific study might have somewhat altered the decision thresholds. Therefore, the generalizability of the characterization of participants is less certain. Hence, although the results of the evaluation of the invitation schemes in paper I, the investigation into risk factors for non-participation in paper III, and the follow-up of the total cohort in paper IV could be perceived as – by design – almost certainly generalizable to the source population, likely generalizable to the entire Swedish population and probably generalizable to most Western populations. The participation (which is the outcome in paper I and III, the "exposure" in paper IV, and a prerequisite for the evaluation in paper II) may differ between populations so that some reservations must be made regarding the external validity.

Selection bias

In a cohort study, selection bias may occur if some correlate of the outcome is capable of influencing the participation in the study and – when two or more exposure categories are compared – this influence is differential across exposure categories *(Greenland 1977)*. This is a fairly uncommon situation in cohort studies because the outcome has generally not yet occurred when the exposure is measured or assigned. However, when the outcome is a behavior based on a habit/attitude or a psychological trait, likely present already at entry, selection bias is possible. Theoretically, this could have occurred in paper I and paper III where the actual *decision* to participate was the outcome, but since all selected individuals were included in the analysis, there was no scope for selection bias. In paper IV, where the exposure of interest was participation, and the outcome was cancer incidence or mortality, selection bias could have influenced the results during the first year or two because subtle symptoms from a yet undiagnosed impending cancer could have affected the decision to accept the screening sigmoidoscopy. If important selection bias would exist, a concentration of colorectal cancers in the first 1-2 years after the invitation would be expected among participating individuals. Although the few colorectal cancer diagnoses in the participants tended to cluster in the first year (3 out of 5 cancers – probably more attributable to the screening than to any selection bias), there was no clear evidence of selection bias, and the number of observed cancers in the non-participating group (16 cancers) was considerably greater than the number in the participants. If, anything, selection bias may have led to a slight underestimation of the difference between non-participants and participants.

The inclination to experience and/or report pain or discomfort in connection with the sigmoidoscopy, as investigated in paper II, could be due to a habit/attitude or a trait that could also potentially have affected the participation. But, since the studied exposures in paper II (two different invitation methods) were assigned at random, possible habits or traits that were linked both to pain sensitivity and to the willingness to participate were almost certainly evenly distributed across the exposure categories of interest. Therefore, the possible selection of people with certain pain behaviors would not introduce any bias and thus not affect the internal validity. On the other hand, the selection could have influenced the external validity (see above).

Information bias

Misclassification of exposure

Although misclassification of the exposure may certainly occur in cohort studies, this misclassification is most commonly non-differential with regard to outcome. Accordingly, information bias in the classical sense (which could shift associations in any direction) is fairly rare in a cohort study, but non-differential misclassification can still affect the measure of association, almost invariably towards the null *(Rothman et al. 1998)*. In our study, the exposure was, in most cases, either distinct and verifiable (e.g., the invitation mode; participation or non-participation) or collected from registers and thereby measured totally independently of the outcome. Consequently, exposure misclassification could frequently either be confidently ruled out or confidently considered to be non-differential. In the former case, the estimates would remain unchanged, while in the latter case, the relative risks would be shifted only towards the null (i.e., a somewhat conservative estimate would be generated).

In paper II, however, information about some "exposures" (expectations and anxiety prior to the endoscopic examination) was collected *after* the sigmoidoscopy and simultaneously with self-ratings of the outcome (subjective pain and discomfort during the examination). One does not have to be a trained epidemiologist to realize that there might be links between the outcome and the accuracy with which the exposure is reported. Thus, there is definitely scope for information bias. It would have been more appropriate to measure prior anxiety *before* the examination.

Misclassification of outcome

Misclassification of the outcome is always a viable possibility in cohort studies, and misclassification that is differential with regard to exposure, leading to information bias, may also have occurred in our study. In paper IV, the "exposure" was the *decision* to participate, and this decision could conceivably be linked to more health conscience, a greater vigilance towards subtle symptoms, and a general readiness to consult doctors. This could lead to that participants were constantly under more intense "surveillance" during the follow-up period than were non-participants. This could have led to some overestimation of the cancer incidence among participants, and some underestimation among non-participants. However, since we found a higher incidence among the non-participants, this could not be attributed to information bias (detection or ascertainment bias). On the contrary, such bias may have led to a too conservative estimate of the difference between participants and non-participants. Information bias with regard to deaths is highly unlikely; first, the Cause of Death Register is essentially complete *(National Board of Health and Welfare 2005b)*, and if there would have been some underreporting, it is inconceivable that it would have been differential with regard to the exposures under study. Also, the Cancer Register is essentially complete *(National Board of Health and Welfare 2006)*, and any misregistration (apart from detection and/or ascertainment bias) would probably be non-differential.

Self-reported data (paper II) constitutes a special case. When the effects of background factors such as personality traits on subjective outcomes (pain, discomfort) are studied, it is conceivable that some of these background factors are associated with variations in the way pain and discomfort is communicated. Therefore, there is definitely a possibility of information bias in these analyses.

In paper I and III, there is limited, if any, scope for misclassification of the outcome (participation or non-participation), while

misclassification of the outcome (endoscopic findings) in paper I was unlikely to be differential with regard to the exposure (invitation method).

Confounding

A confounder is an independent risk factor for the outcome and also associated with the exposure. Confounding occurs when this factor is unevenly distributed between the exposures under study and effects the estimated association. If we know about the confounding and have measured it correctly, we can control for it in the analysis, either with stratification or with regression. Hence, there is a problem with the confounding factors we do not know about (or do not measure). The best way to eliminate confounding is by randomization. With this approach, the confounding factor will be, by design, evenly distributed between the groups, at least when the sample size is large. We used randomization in the studies of the effect of different invitation methods on participation (paper I) and experiences of the sigmoidoscopy (paper II).

In paper III, we found male gender to be associated with an increased risk of non-participation in the regression analysis, but not in the unadjusted analysis. This was due to the confounding effect of the risk factor income that we adjusted for in the regression (Figure 10). There was a positive association of non-participation with low income (low income increased the risk of non-participation [+]), but, since there were considerably less men in the lowest tertile of income (18% [183/1001]), there was also a *negative* (-) association between low income and male gender. If we did not adjust for income in our analysis (together with other possible confounding factors) the difference by gender would have been attenuated.

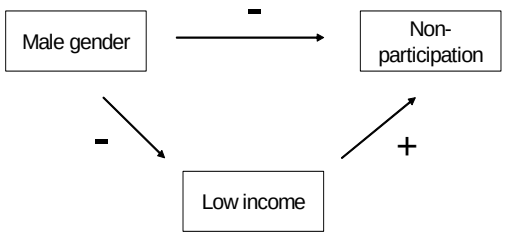

Figure 10. The confounding effect of income on male gender. If not adjusted for, there would be a decreased risk (-) of non-participation with male gender.

The list of potential confounding factors in paper III is long and we have only a small portion included in the final model depending on their significance. We know that confounding exists, since the crude estimates in the unadjusted analysis and the point estimates in the fully adjusted analysis differ to some extent, although they are in the same direction (above or below 1.0).

In paper IV, we adjusted for confounding by gender using regression analysis when we compared participants and non-participants, and controlled for confounding by matching with age, gender and calendar period when we compared with the general Swedish population.

Effect modification

When there was a large difference in participation between the centers (47% in Uppsala and 30% in Lund) we suspected that effect modification (i.e. interaction) could be present. This is not a problem in the design or analysis of our data, but merely reflects the effect the center could have on participation or non-participation in the real situation. Could the associations of the different background factors with non-participation in Uppsala be different from Lund? When we analyzed the data stratified by center we found that the background factors associated with non-participation were the same in Uppsala and in Lund and, thereby, we could rule out the possibility of an effect modified by center.

Paper I vs. paper III

Compiling the computer file with the invitees' national registration numbers – unique personal identifiers assigned to all Swedish residents – to be used in the multiple record linkages (paper III), we found one uninvited man in Lund (group 1) in addition to the 12 reported in paper I, that had moved out of the study area. Moreover, one man in Uppsala (group 1) was deemed uninvited due to no match in the multiple record linkages owing to an erroneous national registration number. This generates 1986 invitees instead of 1988 earlier reported. Seven non-participating men in Uppsala (group 1) were also actually found to be women. The SPAR register did not provide us with the national registration numbers of the invitees and, thereby, not information about gender. In paper I, the non-participants were assigned gender by their first (Christian) name. When the first name did not indicate gender, we performed a search in Name statistics *(Statistics Sweden 2000)* and assigned the subject the gender most represented.

Moreover, one man was misclassified as telephoned by the nurse (group 1), when he was actually asked to make the call himself (group 2), and one woman vice versa. Despite the limited scope for misclassification of the outcome, one man in Uppsala (group 1) and two women in Lund (one from each group) were also misclassified as participant and non-participants, respectively.

However, the misclassification of exposure (two subjects) or outcome (three subjects) and the incorrect gender (7 subjects) has not had any impact on the results in paper I. With 0.6% (12/1986) misclassified subjects in either variable, we would still not get statistical differences in participation by gender or invitation group ($p=0.740$ *vs.* $p=0.632$ and $p=0.185$ *vs.* $p=0.182$, respectively, [χ^2 test]).

Precision

With high precision, the impact of random errors ("by chance") is small and we would get the same results if we performed the study again. The result is "accurate". High precision is generated by a large number of observations and must be considered when designing a study. The larger the sample size, the larger the expected number of observations and, hence, an increased precision.

The precisions in the different papers of our study are expressed with p-values (paper I, II and III) or confidence intervals (paper III and IV). A p-value <0.05 only tells us that there is a risk of less than 5% that our statistically significant results are by chance, but the 95% confidence intervals give us more information; we know, with 95% probability, that the "true" value is within the interval. The value could still be within the interval by chance, but only with a risk of 5%. The width of the interval gives us information of the precision of the study. With a narrow confidence interval, there is less variability of the observations and the precision is high, as compared to a wide interval. Even

with a relatively large sample size (2000 subjects), the observations of the different outcomes measured are in some certain cases minimal. This is most evident in paper IV and – to overcome low precision – we grouped the different outcomes measured into larger categories. For example, the SMR of gastrointestinal cancer among non-participants had a confidence interval of 1.7-5.3 (14 observations), as compared to 0.8-1.5 for mortality from neoplastic diseases (43 observations) (Table 10).

Interpretations and implications of findings

Overall, the participation in our feasibility study of sigmoidoscopy screening was low. Even if 39% is within the range of earlier publications *(Foley 1987; Cockburn et al. 1995; Rasmussen et al. 1999; Thiis-Evensen et al. 1999; Collett et al. 2000; Segnan et al. 2002; UK Flexible Sigmoidoscopy Screening Trial Investigators 2002; Gondal et al. 2003)*, it is close to half of the participation rates of breast *(The Swedish Organised Service Screening Evaluation Group 2006a)* and cervical cancer *(Dillner 2000)* screening in Sweden. Breast- and cervical cancer screening target somewhat younger women (40-74 and 23-60 years old, respectively) and have demonstrated a decrease in compliance with older age *(Smith et al. 1992; Maxwell et al. 2001)*, but this could unlikely be the only explanation to the large difference in compliance noted. As described earlier, low participation decreases the effectiveness of a screening program. While we wait for the results from the RCTs, evaluating the efficacy of sigmoidoscopy screening in reducing colorectal cancer mortality, we must ask ourselves what we can do to increase screening participation.

Modifying the invitation routines

In breast cancer screening, modifying the invitation routines to include a letter of invitation and phone call has been effective in increasing participation *(Bonfill et al. 2001)*. However, we did not see any increased participation among invitees called up by the nurse. Receiving the more personalized invitation with a phone call had no major impact on the experience of the sigmoidoscopy, except for a small, but significant, reduction in "other discomfort". From an economic perspective, perhaps it is advantageous to send out invitations by mail only. As in organized cervical cancer screening in Sweden *(Eaker et al. 2004)*, we found the use of reminders to be very important for participation.

The information about the sigmoidoscopy provided in the invitation letter might have been decisive. When we described the procedure, we also explained that medication would be provided to those experiencing pain during the sigmoidoscopy. With this information, the expectation of a painful procedure could have been exaggerated. We have also speculated upon whether requesting a questionnaire and fecal sample- (the latter after acceptance of the invitation) might influence participation, but this has not been evaluated by randomization. Another factor that might have affected the participation was the mandatory information that this was a research project and, thereby, provides other incentives to participate; some invitees might feel obligated to participate – it is more about altruistically taking part in the project. This would probably have been a larger problem if the invitees were patients in a dependent position, and not randomly selected from the population register as in our study. However, the generalizability of the characterization of the participants and their experiences of the sigmoidoscopy could be limited (see above).

We were bewildered by the remarkable difference in participation between the two screening centers (47% in Uppsala *vs.* 30% in Lund), even after controlling for all studied socio-demographic and health-related variables. Considering the wide range in participation rates experienced in earlier sigmoidoscopy screening studies (23-81% *(Foley 1987; Cockburn et al. 1995; Rasmussen et al. 1999; Thiis-Evensen et al. 1999; Collett et al. 2000; Segnan et al. 2002; UK Flexible Sigmoidoscopy Screening Trial Investigators 2002; Gondal et al. 2003)*), one might argue that the participation rate is low in Lund, but on the other hand, high in Uppsala. Given the ethnic and cultural homogeneity in Sweden, it is unlikely that differences in basic existential values would explain this between-center variation. One difference between the invitations delivered by the centers was that the sigmoidoscopies were offered in the evening in Lund and daytime in Uppsala. This, however, should have had a positive impact on participation *(Cockburn et al. 1995)*. In a questionnaire study of the non-participants (see below), more non-participants declined participation due to work in Uppsala compared to Lund.

Logistical differences in the two secretariats might have been the most important determinant of differences in participation between the centers, but this has not been scientifically evaluated. Irrespective of participation rate, the associations with different background factors are similar in the stratified analysis and combined model adjusted for center. If, for some reason, the low participation in Lund was due to study logistics with non-differential misclassification of the exposure, it would only have attenuated the associations we found. Subtle between-center differences in public confidence in health care might have played a role that we have not been able to evaluate. Both the overall low participation rate and effect of reminders seem to substantiate the importance a formalized organization with a call-recall system and quality assurance for a screening program to be effective *(Faivre et al. 2002)*. Since, with the exception of screening mammography *(Maxwell 2000; Bulliard et al. 2004)*, distance to the center does not seem to affect participation, colorectal cancer screening centers could be centralized to the hospitals, thereby generating larger volumes with better quality.

Reaching the non-participants

Instead of using interviews or self-administered questionnaires, often with low response rates due to lack of motivation, we have been able to obtain robust empiric data, supporting with greater confidence previously published material, that suggests socio-economically underprivileged people are at higher risk of not participating in colorectal screening programs *(Neilson et al. 1995; Sutton et al. 2000; Wardle et al. 2000; McCaffery et al. 2002)*.

The same risk was also seen in unmarried and divorced people and, in contrast to most other screening studies, in men *(Sutton et al. 2000; Weissfeld et al. 2002; Chao et al. 2004; Montano et al. 2004; Slattery et al. 2004; Turner et al. 2004; Denberg et al. 2005)*. People prone to decline participation might not be accessible by regular invitation letters or articles in the local newspaper used in our study (see below), but instead are best targeted by exposure to other media, e.g. television or radio campaigns *(Powe et al. 2006)*. This is speculative, but an opportunity for future research.

Even if we have found background factors associated with non-participation in screening, these factors are only surrogates and not a biological or psychological explanation or actual mechanism explaining *why* these people actually chose not to participate. It is naïve to believe that

merely sending out reminders or radio campaigns would have any major impact on these underlying mechanisms. It is a tentative approach that, most certainly, could increase the participation rate to some extent, but we do not know actually *why* this was achieved.

As we did not find any practical (e.g. distance to the screening center) or medical (e.g. hospitalizations) obstacles for participation, our results seem to converge upon motivation as a critical factor and stress the importance of motivating screening in individuals who might otherwise be prone to ignore invitations. This is probably applicable to other settings, besides colorectal cancer screening, since the associations we found with non-participation have been demonstrated in a variety of different public health surveys *(Korkeila et al. 2001; Turrell et al. 2003)*, as well as in smoking treatment services *(Ferguson et al. 2005)*.

Results from a questionnaire study of non-participants

Outside the scope of this thesis, in an attempt to understand the reasons for declining participation, non-participants were asked to anonymously complete a questionnaire with questions regarding reasons for not participating. This anonymous questionnaire gave a low overall response rate. Consequently, any results would contain a higher risk of selection bias, information bias and a low validity (see above). Still, with the selection of responders in mind, the anonymous questionnaire study deserves some attention.

In total 36% (435/1215) answered the questionnaire; significantly more women than men (41% *vs.* 30%, χ^2=7.40, p<0.01). The most common reason for declining participation was that the sigmoidoscopy seemed unpleasant (33% [142/435]) (Table 13).

Table 13. Reasons for declining sigmoidoscopy screening in 36% (435/1215)[*] of men and women anonymously answering a mailed questionnaire[†]

Variable	Total frequency (%)[‡]	Frequency women (n=241) (%)[‡]	Frequency men (n=182) (%)[‡]	P-value[§]
Examination uncomfortable	142 (33%)	91 (38%)	47 (26%)	0.08
Did not want to	95 (22%)	49 (20%)	47 (26%)	0.35
Checked up by other doctor	70 (16%)	35 (15%)	32 (18%)	0.55
Did not have time	69 (16%)	43 (18%)	26 (14%)	0.48
Other disease	57 (13%)	34 (14%)	23 (13%)	0.81
Hospitalized	8 (2%)	5 (2%)	3 (2%)	0.96
Other reason	98 (23%)	59 (24%)	36 (20%)	0.42

[*] 12 out of 435 (3%) responses did not report gender.
[†] More than one alternative could be chosen.
[‡] The relative frequency adds up to >100% due to more than one alternative chosen.
[§] Estimated with χ^2 test.

Seventy-three per cent (318/435) of the non-participants graded the value of a screening sigmoidoscopy on a VAS scale (0-100 mm). The graded answers were cate-gorized into three groups; 41% (129/318) found it without particular value (VAS 0-39), 32% (101/318) had indistinct answer (VAS 40-79) and 28% (88/318) found it valuable (VAS 80-100).

Overall, the frequency of bowel symptoms was graded very low; the median VAS was <1 for stomach pain, change in stool habits, diarrhea, and blood in stool. Absence of symptoms could strengthen the opinion of a good health status and a low perceived susceptibility to colorectal cancer *(McCaffery et al. 2001)*. Consequently, the screening sigmoid-oscopy could have been regarded as unnecessary.

Seventy eight per cent (329/422) did not have a problem getting to the hospital. Two thirds (62/93) of the subjects reporting such a problem, had difficulties due to work. This was the only statistical significant difference between the centers, with more subjects declining due to work in Uppsala (38 subjects) than in Lund (24 subjects) (p=0.02). With these selective results in mind, maybe a more flexible appointment schedule would have been appropriate.

Awareness of self-selection to screening

We have demonstrated an increased risk of specific cancer and death among non-participants in sigmoidoscopy screening, as compared to participants. Our inter-pretation is that the main driving force behind the observed differences is not the effect of screening *per se*, but rather the self-selection. The higher incidence of smoking-related cancers and mortality from circulatory diseases, among non-participants, relative to participants, supports the hypothesis of an "unhealthy" lifestyle among the non-participants *(Shapiro et al. 2001; Slattery et al. 2004)*. Participants, on the other hand, have been shown to have a healthy lifestyle *(Larsen et al. 2006)* and in our study they had significant decreased risks, relative to the matching general population, e.g. a decreased risk by 50% for all-cause mortality, and by 40% for mortality from cancer.

Observed differences in the selected cancers and deaths are probably due to different risks at baseline (invitation) – factors we have not been able to examine. Low socio-economic status, though, has been shown to increase the risk of overall morbidity and mortality *(Mackenbach et al. 1997; Sorlie et al. 1995)*, and mortality from cancer *(Hart et al. 2001; Bouchardy et al. 2006; Shaw et al. 2006)* and circulatory diseases *(Kunst et al. 1999; Avendano et al. 2005; Avendano et al. 2006)*, specifically.

Even if we argue that the differences observed are due to self-selection, we can-not rule out the possibility that sigmoid-oscopy screening has, in fact, had an effect on the different outcomes measured. With the few colorectal cancers we observed (5 and 16 among participants and non-participants, respectively), it would be overzealous to say that there is a decrease in colorectal cancer mortality (0 and 7 among participants and non-participants, respectively [not shown in Table 9]), due to the sigmoidoscopy screening. More reasonable, though, some participants with a false positive test (e.g. a hyperplastic polyp) may have changed to an even healthier life-style, e.g. stopped smoking, and hereby prevented death from a circulatory disease. Since disease development is a long process, the possible effect of screening might even be larger with time. Unfortunately, due to our study design, we will not be able to determine this.

The benefit of participation, irrespective of baseline risk, has been demonstrated in Swedish mammography screening services *(The Swedish Organised Service Screening Evaluation Group 2006a, b)*, which, however, have a participation rate of 75%. A high participation rate in colorectal cancer screening is essential to limiting the effect of self-selection. Self-selection could attenuate the cost-effectiveness of a screening program on a population level.

Information to the public and the invitees

Speculatively, the difference in participation between Uppsala and Lund might have been due to a temporary difference in public awareness regarding the potential benefits of cancer screening. There was an article covering the study in the leading local newspaper in Uppsala but not in Lund. Since awareness about colorectal cancer is low *(Wong et al. 2002; McCaffery et al. 2003; Keighley et al. 2004; Wee et al. 2005)*, our results suggest that much attention should also be paid to the information given. The information must appeal to men, people who are unmarried or divorced, and people with low socio-economic status in particular.

Enclosing a more thorough health education leaflet, along with the actual invitation, would probably also be advantageous, since it has been demonstrated that enhancing the knowledge of colorectal cancer as well as the potential benefits of screening can increase the likelihood of participation in screening *(Hart et al. 1997)*. The information about the actual sigmoidoscopy examination in the invitation letter could be an important factor. In the eyes of a potential participant, there might not be any decisive difference between a sigmoidoscopy and a complete colonoscopy. Accordingly, as presented above, from the questionnaire study of non-participants, the most common reason for declining participation was that the sigmoidoscopy seemed unpleasant. Speculatively, with the selection of subjects participating in mind, the non-participants would have been more prone to participate if they had received more information about previous participants' experiences of sigmoidoscopy, but also, if they had had the opportunity to choose between the various tests recommended in the U.S. *(Smith R.A. et al. 2001; Winawer et al. 2003)*. If the sigmoidoscopy was regarded as unpleasant, a FOBT might have been a reasonable alternative.

Improving the sigmoidoscopy examination

However, not all participants experienced the sigmoidoscopy as innocuous. There were significant associations with pain and other discomfort during the sigmoidoscopy with apprehension regarding long examination time and anxiety during the examination. Our results suggest that reassurance and frequent evacuation of air from the bowel during the examination could be a way of reducing pain.

In average, our sigmoidoscopies were quick. This could be attributed to the fact that no biopsies were performed during the procedure, as well as good bowel preparation. Bowel preparation with a rectal enema only is deemed sufficient *(Cockburn et al. 1995)*, but the lower sensitivity with sigmoidoscopy, as compared with colonoscopy, has been attributed to the less effective bowel preparation *(Winawer et al. 2003)*. Motivating proper bowel preparation could be the key to a successful examination.

Even though the study was not designed to evaluate the accuracy of sigmoidoscopy, it is striking to note that, despite the fact that experienced colorectal surgeons performed most of our sigmoidoscopies, none of the three cases of adenocarcinoma (and two *in situ*) was suspected at the time of

sigmoidoscopy. They were instead detected as a result of our criteria for follow-up colonoscopy (suspected cancer, adenoma or >3 hyperplastic polyps). So, in our design with no biopsies at sigmoidoscopy, it was the follow-up colonoscopy that was important. Otherwise, in theory, the sensitivity for colorectal cancer would have been 0%. The difficulty in the macroscopic assessment of colorectal lesions was further demonstrated in the histopathological reports, where subjects with suspected benign hyperplastic polyps actually had true adenomas and vice versa. Obtaining tissue samples at the time of sigmoidoscopy would probably have been in order.

Ethical aspects of non-participation

When discussing participation in screening programs and the potential interventions to increase compliance, it is important to remember that the decision to decline is very individual. Of course, there could be a lack of information etc. that we are responsible to communicate, but in some circumstances the decision is probably due to a personal preference that we must respect. There could be existential questions involved, e.g., the necessity to prolong life, the individual apprehension of mortality, and priorities in life in general. This should be considered before enthusiastically starting to invite people to a screening program.

Future perspectives

The effectiveness of different colorectal cancer screening tests must be evaluated. If randomized controlled trials demonstrate a reduction in mortality with sigmoidoscopy, the problem of low compliance must be given priority. If we could improve enrollment of non-participants, sigmoidoscopy could be a tentative screening method. Efforts to motivate presumptive non-participants must be made. Not only local newspapers, television and radio might be an effective strategy to increase participation but the internet could also help reach non-participants and inform the public in general.

The European Union recommends it's member states' organized CRC screening *(Boyle et al. 2003)*. While we are waiting for "the perfect test", introducing any of the recommended screening tests in a population based program is probably better than doing nothing at all, but the effectiveness must evaluated in a randomized setting.

More studies are needed, not only regarding the negative psychological effects of getting a false positive test result and the corresponding impact on quality of life, but also to evaluate eventual changes in life-style after a screening test. Moreover, as we do not know *why* the non-participants actually declined participation, there is a need for more research into potentially modifiable social and psychological mechanisms behind non-participation. Within a larger randomized trial evaluating the effectiveness of screening, a nested randomized study could then be performed to evaluate different interventions assigned to increase participation. The between-center variation also points to a need for intensified research at the community level regarding the impact of logistics on participation in screening.

CONCLUSIONS

- In our population-based feasibility study of sigmoidoscopy screening, the compliance was lower and the adenomas were fewer than expected. A more personalized invitation did not increase screening uptake.

- Participants tolerated the preparations and the actual examinations well, the time expenditure was acceptable and the technical failures low. Flexible sigmoidoscopy is feasible in colorectal cancer screening if participation is not hampered by perceptions about the sigmoidoscopy *per se*.

- Our unbiased background information about *all* participants and non-participants invited to colorectal cancer screening with sigmoidoscopy, demonstrates with considerably greater confidence than previously published material, that men, unmarried or divorced people, and people with low socio-economic status are at highest risk of non-participation. To increase participation, invitations must appeal to these groups.

- Complete register-based follow-up of both participants and non-participants unveiled a general tendency for higher incidence rates of gastrointestinal – including colorectal – cancers, and significantly higher mortality from these cancers, cancer overall, as well as elevated all-cause mortality, among non-participants, most likely due to self-selection.

POPULÄRVETENSKAPLIG SAMMANFATTNING (POPULAR SCIENCE SUMMARY IN SWEDISH)

Tjocktarmscancer är den tredje vanligaste cancerformen i Sverige och drabbar mer än 5500 personer varje år. Sjukdomen är lämplig för screening (riktad hälsoundersökning) av befolkningen, då den bl.a. i många fall leder till hög sjuklighet och risk för tidigare död samt det finns botande behandling att ge om man hittar tjocktarmscancer i ett tidigt stadium.

Vi har genomfört en pilotstudie på tvåtusen 60-åringar från Uppsala och Lund som slumpades ur folkbokföringsregistret. De bjöds in till att undersökas med en böjlig tarmkikare (sigmoideoskop) för att hitta cancer eller förstadier till cancer. Hälften blev uppringda av en sjuksköterska för att boka tid för undersökningen och hälften blev ombedda att själva ta kontakt. Efter undersökningarna samkörde vi alla inbjudna mot olika register för att ta reda på avidentifierad bakgrundsinformation och förekomst av cancer och död under uppföljningstiden. Syftet med studien har varit att se hur inbjudan mottas, utvärdera fynd och tekniska detaljer kring undersökningen och att studera om de som väljer att inte delta i screeningen skiljer sig från dem som deltar. Syftet har däremot inte varit att utvärdera om screening med tarmkikare leder till minskad död i tjocktarmscancer.

Totalt 771 personer deltog (39%). Vi såg ingen skillnad i deltagandet när det gäller inbjudningsförfarande. Åttioåtta personer (11%) hade förändringar som ledde till ytterligare undersökningar (koloskopi). Tre personer som deltog visade sig ha cancer. Efter en noggrann tarmrengöring tog screeningundersökningen mindre än 10 minuter. Överlag upplevde de som deltog undersökningen som positiv. Bland dem som valde att inte delta fanns män, ogifta och frånskilda och de med låg inkomst överrepresenterade. Tjocktarmscancer i släkten ledde till en ökad benägenhet att delta, medan avstånd till sjukhuset inte hade någon inverkan på deltagandet. Efter totalt 9 års uppföljning hade de som inte deltagit en ökad förekomst av bl.a. mag/tarm-, lung- och annan rökningsrelaterad cancer, jämfört med dem som deltog. Exempelvis var risken för att ha fått diagnosen tjocktarmscancer mer än dubbelt så stor, men eftersom relativt få fall upptäcktes under uppföljningstiden (totalt 21 tjocktarmscancrar) så är resultatet inte statistiskt signifikant. Däremot var det bland ”icke-deltagarna” statistiskt signifikant ökad risk med 90% för död i cancer, med 130% för död i hjärt-kärlsjukdom och med 140% för död oavsett orsak, jämfört med deltagarna. Den ökade risken för cancerdöd kvarstod då vi räknade bort dem som hade fått en cancerdiagnos inom 5 år före inbjudan. Jämfört med populationen i Sverige med samma ålders- och könsfördelning, hade ”icke-deltagarna” överlag en ökad risk och deltagarna överlag en *minskad* risk för de studerade cancrarna och för död. Exempelvis hade deltagarna statistiskt signifikant minskad risk med 40% för död i cancer och med 50% för död oavsett orsak jämfört med populationen i Sverige.

Färre personer än vi hade förväntat oss deltog. Ett högt deltagande är en förutsättning för att man i en större s.k. randomiserad studie ska kunna utvärdera effekterna av en folkhälsoundersökning riktad mot tjocktarmscancer. Även om vi inte vet *varför* dessa grupper (män, ogifta o.s.v.) har en ökad risk för att inte delta, så tror vi att mer information, särskilt riktad mot dem med låg socioekonomisk status, är viktigt för att nå ett högt deltagande. Skillnaderna i cancer och död under uppföljningstiden bedömer vi bero på det urval av personer som väljer att delta i folkhälsoundersökningar. Deltagarna är sannolikt mer

hälsomedvetna och förhållandevis friska personer och kanske inte de som drar mest nytta av att delta.

Vid större försök med populationsbaserade folkhälsoundersökningar riktade mot tjocktarmscancer, likt det projekt som planeras i Stockholm med test för blod i avföringen *(Dagens Nyheter 2006)*, är det viktigt att optimera deltagandet. Högt deltagande minskar effekterna av att friskare personer i större utsträckning väljer att delta. Utan ett högt deltagande riskerar folkhälsoundersökningar riktade mot tjocktarmscancer att ur ett hälsoekonomiskt perspektiv fallera.

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REFERENCES

Ahlquist, D. A., Skoletsky, J. E., Boynton, K. A., Harrington, J. J., Mahoney, D. W., Pierceall, W. E., *et al. (2000)*. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. Gastroenterology 119(5): 1219-27.

Andersson, S., Dillner, L., Elfgren, K., Mints, M., Persson, M. and Rylander, E. *(2005)*. A comparison of the human papillomavirus test and Papanicolaou smear as a second screening method for women with minor cytological abnormalities. Acta Obstet Gynecol Scand 84(10): 996-1000.

Armitage, N. *(1997)*. Screening for cancer. In: Morris, D., Kearsley, J., Williams, C., (eds) Cancer: a comprehensive clinical guide, Taylor & Francis Ltd (UK), pp 9-20.

Atkin, W. S., Cuzick, J., Northover, J. M. and Whynes, D. K. *(1993)*. Prevention of colorectal cancer by once-only sigmoidoscopy. Lancet 341(8847): 736-40.

Avendano, M., Kunst, A. E., Huisman, M., Lenthe, F. V., Bopp, M., Regidor, E., *et al. (2006)*. Socioeconomic status and ischaemic heart disease mortality in 10 western European populations during the 1990s. Heart 92(4): 461-7.

Avendano, M., Kunst, A. E., van Lenthe, F., Bos, V., Costa, G., Valkonen, T., *et al. (2005)*. Trends in socioeconomic disparities in stroke mortality in six European countries between 1981-1985 and 1991-1995. Am J Epidemiol 161(1): 52-61.

Birgisson, H., Talback, M., Gunnarsson, U., Påhlman, L. and Glimelius, B. *(2005)*. Improved survival in cancer of the colon and rectum in Sweden. Eur J Surg Oncol 31(8): 845-53.

Bonfill, X., Marzo, M., Pladevall, M., Marti, J. and Emparanza, J. I. *(2001)*. Strategies for increasing women participation in community breast cancer screening. Cochrane Database Syst Rev(1): CD002943.

Bouchardy, C., Verkooijen, H. M. and Fioretta, G. *(2006)*. Social class is an important and independent prognostic factor of breast cancer mortality. Int J Cancer 119(5): 1145-51.

Boyle, P., Autier, P., Bartelink, H., Baselga, J., Boffetta, P., Burn, J., *et al. (2003)*. European Code Against Cancer and scientific justification: third version (2003). Ann Oncol 14(7): 973-1005.

Brevinge, H., Lindholm, E., Buntzen, S. and Kewenter, J. *(1997)*. Screening for colorectal neoplasia with faecal occult blood testing compared with flexible sigmoidoscopy directly in a 55-56 years' old population. Int J Colorectal Dis 12(5): 291-5.

Bruhn, Å., Statistics Sweden *(2004)*. Personal Communication. December 2nd.

Bulliard, J. L., de Landtsheer, J. P. and Levi, F. *(2004)*. Profile of women not attending in the Swiss Mammography Screening Pilot Programme. Breast 13(4): 284-9.

Cappell, M. S. and Forde, K. A. *(1989)*. Spatial clustering of multiple hyperplastic, adenomatous, and malignant colonic polyps in individual patients. Dis Colon Rectum 32(8): 641-52.

Chao, A., Connell, C. J., Cokkinides, V., Jacobs, E. J., Calle, E. E. and Thun, M. J. *(2004)*. Underuse of screening sigmoidoscopy and colonoscopy in a large cohort of US adults. Am J Public Health 94(10): 1775-81.

Cheong, Y., Farrow, R., Frank, C. S. and Stevenson, G. W. *(1998)*. Utility of flexible sigmoidoscopy as an adjunct to double-contrast barium enema examination. Abdom Imaging 23(2): 138-40.

Cockburn, J., Thomas, R. J., McLaughlin, S. J. and Reading, D. *(1995)*. Acceptance of screening for colorectal cancer by flexible sigmoidoscopy. J Med Screen 2(2): 79-83.

Collett, J. A., Olynyk, J. K. and Platell, C. F. *(2000)*. Flexible sigmoidoscopy screening for colorectal cancer in average-risk people: update of a community-based project. Med J Aust 173(9): 463-6.

Dagens Nyheter (2006). Cancer i tjocktarmen söks med screening. December 13th.

Dafnis, G., Ekbom, A., Påhlman, L. and Blomqvist, P. *(2001)*. Complications of diagnostic and therapeutic colonoscopy within a defined population in Sweden. Gastrointest Endosc 54(3): 302-9.

Debatin, J. F. and Lauenstein, T. C. *(2003)*. Virtual magnetic resonance colonography. Gut 52 Suppl 4: iv17-22.

Delco, F., Egger, R., Bauerfeind, P. and Beglinger, C. *(2005)*. Hospital health care resource utilization and costs of colorectal cancer during the first 3-year period following diagnosis in Switzerland. Aliment Pharmacol Ther 21(5): 615-22.

Denberg, T. D., Melhado, T. V., Coombes, J. M., Beaty, B. L., Berman, K., Byers, T. E., *et al. (2005)*. Predictors of nonadherence to screening colonoscopy. J Gen Intern Med 20(11): 989-95.

Dent, O. F., Bartrop, R., Goulston, K. J. and Chapuis, P. H. *(1983)*. Participation in faecal occult blood screening for colorectal cancer. Soc Sci Med 17(1): 17-23.

Dillner, J. *(2000)*. Cervical cancer screening in Sweden. Eur J Cancer 36(17): 2255-9.

Duke University (1999). Evaluation of cervical cytology. Rockville, Md.: Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, 1999; AHCPR publication no. 99-E010 (Evidence report/technology assessment no. 5).

Eaker, S., Adami, H. O., Granath, F., Wilander, E. and Sparen, P. *(2004)*. A large population-based randomized controlled trial to increase attendance at screening for cervical cancer. Cancer Epidemiol Biomarkers Prev 13(3): 346-54.

Eaker, S., Adami, H. O. and Sparen, P. *(2001a)*. Reasons women do not attend screening for cervical cancer: a population-based study in Sweden. Prev Med 32(6): 482-91.

Eaker, S., Adami, H. O. and Sparen, P. *(2001b)*. Attitudes to screening for cervical cancer: a population-based study in Sweden. Cancer Causes Control 12(6): 519-28.

Faivre, J., Bouvier, A. M. and Bonithon-Kopp, C. *(2002)*. Epidemiology and screening of colorectal cancer. Best Pract Res Clin Gastroenterol 16(2): 187-99.

Farrands, P. A., Hardcastle, J. D., Chamberlain, J. and Moss, S. *(1984)*. Factors affecting compliance with screening for colorectal cancer. Community Med 6(1): 12-9.

Fearon, E. R. and Vogelstein, B. *(1990)*. A genetic model for colorectal tumorigenesis. Cell 61(5): 759-67.

Feinberg, E. J., Steinberg, W. M., Banks, B. L. and Henry, J. P. *(1990)*. How long to abstain from eating red meat before fecal occult blood tests. Ann Intern Med 113(5): 403-4.

Ferguson, J., Bauld, L., Chesterman, J. and Judge, K. *(2005)*. The English smoking treatment services: one-year outcomes. Addiction 100 Suppl 2: 59-69.

Foley, D. P., O´Brien, M., Crowe, J., O´Callaghan, T.W., Lennon, J.R. *(1987)*. Left-sided colonoscopy as screening procedure for colorectal neoplasia in asymtomatic volunteers. Gut 28: A1367.

Glasziou, P. P. *(1992)*. Meta-analysis adjusting for compliance: the example of screening for breast cancer. J Clin Epidemiol 45(11): 1251-6.

Gluecker, T. M., Johnson, C. D., Harmsen, W. S., Offord, K. P., Harris, A. M., Wilson, L. A., *et al. (2003)*. Colorectal cancer screening with CT colonography, colonoscopy, and double-contrast barium enema examination: prospective assessment of patient perceptions and preferences. Radiology 227(2): 378-84.

Gondal, G., Grotmol, T., Hofstad, B., Bretthauer, M., Eide, T. J. and Hoff, G. *(2003)*. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. Scand J Gastroenterol 38(6): 635-42.

Gotzsche, P. C. and Nielsen, M. *(2006)*. Screening for breast cancer with mammography. Cochrane Database Syst Rev(4): CD001877.

Greenland, S. *(1977)*. Response and follow-up bias in cohort studies. Am J Epidemiol 106(3): 184-7.

Haglind, E. and Lindholm, E. *(2005)*. Unpublished data. Personal Communication with The Cochrane Collaboration in September.

Hakama, M., Hoff, G., Kronborg, O. and Påhlman, L. *(2005)*. Screening for colorectal cancer. Acta Oncol 44(5): 425-39.

Harlan, L. C., Bernstein, A. B. and Kessler, L. G. *(1991)*. Cervical cancer screening: who is not screened and why? Am J Public Health 81(7): 885-90.

Hart, A. R., Barone, T. L. and Mayberry, J. F. *(1997)*. Increasing compliance with colorectal cancer screening: the development of effective health education. Health Educ Res 12(2): 171-80.

Hart, C. L., Hole, D. J., Gillis, C. R., Smith, G. D., Watt, G. C. and Hawthorne, V. M. *(2001)*. Social class differences in lung cancer mortality: risk factor explanations using two Scottish cohort studies. Int J Epidemiol 30(2): 268-74.

Hewitson, P., Glasziou, P., Irwig, L., Towler, B. and Watson, E. *(2007)*. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev(1): CD001216.

Houts, P. S., Wojtkowiak, S. L., Simmonds, M. A., Weinberg, G. B. and Heitjan, D. F. *(1991)*. Using a state cancer registry to increase screening behaviors of sisters and daughters of breast cancer patients. Am J Public Health 81(3): 386-8.

Imperiale, T. F., Ransohoff, D. F., Itzkowitz, S. H., Turnbull, B. A. and Ross, M. E. *(2004)*. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 351(26): 2704-14.

Imperiale, T. F., Wagner, D. R., Lin, C. Y., Larkin, G. N., Rogge, J. D. and Ransohoff, D. F. *(2000)*. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 343(3): 169-74.

Infodata (2007). Vad är SPAR [cited 2007 May]? (In Swedish). Stockholm, Sweden. Available from: http://www.infodata.se/upload/pdf/spar.pdf

Ioannou, G. N., Chapko, M. K. and Dominitz, J. A. *(2003)*. Predictors of colorectal cancer screening participation in the United States. Am J Gastroenterol 98(9): 2082-91.

Johnson, C. D. and Ahlquist, D. A. *(1999)*. Computed tomography colonography (virtual colonoscopy): a new method for colorectal screening. Gut 44(3): 301-5.

Kealey, S. M., Dodd, J. D., MacEneaney, P. M., Gibney, R. G. and Malone, D. E. *(2004)*. Minimal preparation computed tomography instead of barium enema/colonoscopy for suspected colon cancer in frail elderly patients: an outcome analysis study. Clin Radiol 59(1): 44-52.

Keighley, M. R., O'Morain, C., Giacosa, A., Ashorn, M., Burroughs, A., Crespi, M., *et al. (2004)*. Public awareness of risk factors and screening for colorectal cancer in Europe. Eur J Cancer Prev 13(4): 257-62.

Kellokumpu, I. and Kyllonen, L. *(1991)*. Multiple adenomas and synchronous hyperplastic polyps as predictors of metachronous colorectal adenomas. Ann Chir Gynaecol 80(1): 30-5.

Kewenter, J., Brevinge, H., Engaras, B., Haglind, E. and Ahren, C. *(1994)*. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects. Scand J Gastroenterol 29(5): 468-73.

Klabunde, C. N., Schenck, A. P. and Davis, W. W. *(2006)*. Barriers to colorectal cancer screening among Medicare consumers. Am J Prev Med 30(4): 313-9.

Korkeila, K., Suominen, S., Ahvenainen, J., Ojanlatva, A., Rautava, P., Helenius, H., *et al. (2001)*. Non-response and related factors in a nation-wide health survey. Eur J Epidemiol 17(11): 991-9.

Kronborg, O., Fenger, C., Olsen, J., Jorgensen, O. D. and Sondergaard, O. *(1996)*. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 348(9040): 1467-71.

Kronborg, O., Jorgensen, O. D., Fenger, C. and Rasmussen, M. *(2004)*. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol 39(9): 846-51.

Kunst, A. E., Groenhof, F., Andersen, O., Borgan, J. K., Costa, G., Desplanques, G., *et al. (1999)*. Occupational class and ischemic heart disease mortality in the United States and 11 European countries. Am J Public Health 89(1): 47-53.

Lagerlund, M., Hedin, A., Sparen, P., Thurfjell, E. and Lambe, M. *(2000)*. Attitudes, beliefs, and knowledge as predictors of nonattendance in a Swedish population-based mammography screening program. Prev Med 31(4): 417-28.

Lampinen, J. S. and Rannikko, S. *(1999)*. Patient specific doses used to analyse the optimum dose delivery in barium enema examinations. Br J Radiol 72(864): 1185-95.

Larsen, I. K., Grotmol, T., Almendingen, K. and Hoff, G. *(2006)*. Lifestyle characteristics among participants in a Norwegian colorectal cancer screening trial. Eur J Cancer Prev 15(1): 10-9.

Larsen, L. P. and Olesen, F. *(1996)*. Characteristics of subgroups of attenders and non-attenders in an organised screening programme for cervical cancer. J Med Screen 3(3): 133-9.

Leivo, T., Sintonen, H., Tuominen, R., Hakama, M., Pukkala, E. and Heinonen, O. P. *(1999)*. The cost-effectiveness of nationwide breast carcinoma screening in Finland, 1987-1992. Cancer 86(4): 638-46.

Levin, T. R., Palitz, A., Grossman, S., Conell, C., Finkler, L., Ackerson, L., *et al. (1999)*. Predicting advanced proximal colonic neoplasia with screening sigmoidoscopy. JAMA 281(17): 1611-7.

Levitz, J. S., Bradley, T. P. and Golden, A. L. *(2004)*. Overview of smoking and all cancers. Med Clin North Am 88(6): 1655-75, xiii.

Lidbrink, E., Frisell, J., Brandberg, Y., Rosendahl, I. and Rutqvist, L. E. *(1995)*. Nonattendance in the Stockholm mammography screening trial: relative mortality and reasons for nonattendance. Breast Cancer Res Treat 35(3): 267-75.

Lieberman, D. A. and Weiss, D. G. *(2001)*. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. N Engl J Med 345(8): 555-60.

Lieberman, D. A., Weiss, D. G., Bond, J. H., Ahnen, D. J., Garewal, H. and Chejfec, G. *(2000)*. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 343(3): 162-8.

Luboldt, W., Bauerfeind, P., Wildermuth, S., Marincek, B., Fried, M. and Debatin, J. F. *(2000)*. Colonic masses: detection with MR colonography. Radiology 216(2): 383-8.

Mackenbach, J. P., Kunst, A. E., Cavelaars, A. E., Groenhof, F. and Geurts, J. J. *(1997)*. Socioeconomic inequalities in morbidity and mortality in western Europe. The EU Working Group on Socioeconomic Inequalities in Health. Lancet 349(9066): 1655-9.

Macrae, F. A. and St John, D. J. *(1982)*. Relationship between patterns of bleeding and Hemoccult sensitivity in patients with colorectal cancers or adenomas. Gastroenterology 82(5 Pt 1): 891-8.

Mahlck, C. G., Jonsson, H. and Lenner, P. *(1994)*. Pap smear screening and changes in cervical cancer mortality in Sweden. Int J Gynaecol Obstet 44(3): 267-72.

Malila, N., Anttila, A. and Hakama, M. *(2005)*. Colorectal cancer screening in Finland: details of the national screening programme implemented in Autumn 2004. J Med Screen 12(1): 28-32.

Mandel, J. S., Bond, J. H., Church, T. R., Snover, D. C., Bradley, G. M., Schuman, L. M., *et al. (1993)*. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 328(19): 1365-71.

Mandel, J. S., Church, T. R., Ederer, F. and Bond, J. H. *(1999)*. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 91(5): 434-7.

Maxwell, A. J. *(2000)*. Relocation of a static breast screening unit: a study of factors affecting attendance. J Med Screen 7(2): 114-5.

Maxwell, C. J., Bancej, C. M., Snider, J. and Vik, S. A. *(2001)*. Factors important in promoting cervical cancer screening among Canadian women: findings from the 1996-97 National Population Health Survey (NPHS). Can J Public Health 92(2): 127-33.

McCaffery, K., Borril, J., Williamson, S., Taylor, T., Sutton, S., Atkin, W., *et al. (2001)*. Declining the offer of flexible sigmoidoscopy screening for bowel cancer: a qualitative investigation of the decision-making process. Soc Sci Med 53(5): 679-91.

McCaffery, K., Wardle, J., Nadel, M. and Atkin, W. *(2002)*. Socioeconomic variation in participation in colorectal cancer screening. J Med Screen 9(3): 104-8.

McCaffery, K., Wardle, J. and Waller, J. *(2003)*. Knowledge, attitudes, and behavioral intentions in relation to the early detection of colorectal cancer in the United Kingdom. Prev Med 36(5): 525-35.

McGovern, P. M., Gross, C. R., Krueger, R. A., Engelhard, D. A., Cordes, J. E. and Church, T. R. *(2004)*. False-positive cancer screens and health-related quality of life. Cancer Nurs 27(5): 347-52.

Mendelson, R. M., Kelsey, P. J. and Chakera, T. *(1995)*. A combined flexible sigmoidoscopy and double-contrast barium enema service: initial experience. Abdom Imaging 20(3): 238-41.

Montano, D. E., Selby, J. V., Somkin, C. P., Bhat, A. and Nadel, M. *(2004)*. Acceptance of flexible sigmoidoscopy screening for colorectal cancer. Cancer Detect Prev 28(1): 43-51.

Mulder, S. A., Van Leerdam, M. E., Ouwendijk, R. J., Bac, D. J., Giard, R. W. and Kuipers, E. J. *(2007)*. Attendance at surveillance endoscopy of patients with adenoma or colorectal cancer. Scand J Gastroenterol 42(1): 66-71.

Muller, A. D. and Sonnenberg, A. *(1995)*. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 123(12): 904-10.

Muto, T., Bussey, H. J. and Morson, B. C. *(1975)*. The evolution of cancer of the colon and rectum. Cancer 36(6): 2251-70.

National Board of Health and Welfare (1996). Cancer Incidence in Uppsala län and Skåne län 1996 [cited 2007 April]. Stockholm, Sweden. Available from: http://www.socialstyrelsen.se/Statistik/statistikdatabas/

National Board of Health and Welfare (2002). Mammografi - frågor och svar [cited 2007 April]. (In Swedish). Stockholm, Sweden. Available from: http://www.sos.se/FULLTEXT/114/2002-114-5/2002-114-5.htm

National Board of Health and Welfare (2005a). Hospital Discharge Register [cited 2006 April]. Stockholm, Sweden. Available from: http://www.socialstyrelsen.se/Statistik/statistik_amne/sluten_vard/patientregistret+engelsk.htm

National Board of Health and Welfare (2005b). Causes of Death Register [cited 2006 August]. Stockholm, Sweden. Available from: http://www.socialstyrelsen.se/NR/rdonlyres/A6DB1C7C-D106-4413-B8DB-C7C3F3229542/5464/2006423.pdf

National Board of Health and Welfare (2006). Cancer Register [cited 2006 April]. Stockholm, Sweden. Available from: http://www.socialstyrelsen.se/NR/rdonlyres/A23BCC9E-23B5-4747-AAA9-23BB9CDF4B75/4753/20054291.pdf

National Board of Health and Welfare (Socialstyrelsen) (2007a). Cancer Incidence in Sweden 2005 [cited 2007 April]. Stockholm, Sweden. Available from: http://www.socialstyrelsen.se/NR/rdonlyres/FD7B695E-A55F-41F4-B539-4C63D8199601/7192/2007423.pdf

National Board of Health and Welfare (2007b). National Guidelines for breast-, colorectal- and prostate cancer [cited 2007 April]. Stockholm, Sweden. Available from: http://www.socialstyrelsen.se/NR/rdonlyres/93FBE4B3-F64B-402B-918A-88513909BE76/7342/200710291.pdf

NCI Breast Cancer Screening Consortium (1990). Screening mammography: a missed clinical opportunity? Results of the NCI Breast Cancer Screening Consortium and National Health Interview Survey Studies. JAMA 264(1): 54-8.

Neale, A. V., Demers, R. Y. and Herman, S. *(1989)*. Compliance with colorectal cancer screening in a high-risk occupational group. J Occup Med 31(12): 1007-12.

Neilson, A. R. and Whynes, D. K. *(1995)*. Determinants of persistent compliance with screening for colorectal cancer. Soc Sci Med 41(3): 365-74.

Newcomb, P. A., Norfleet, R. G., Storer, B. E., Surawicz, T. S. and Marcus, P. M. *(1992)*. Screening sigmoidoscopy and colorectal cancer mortality. J Natl Cancer Inst 84(20): 1572-5.

Ng, C. S., Doyle, T. C., Courtney, H. M., Campbell, G. A., Freeman, A. H. and Dixon, A. K. *(2004)*. Extracolonic findings in patients undergoing abdomino-pelvic CT for suspected colorectal carcinoma in the frail and disabled patient. Clin Radiol 59(5): 421-30.

Nusko, G., Mansmann, U., Altendorf-Hofmann, A., Groitl, H., Wittekind, C. and Hahn, E. G. *(1997)*. Risk of invasive carcinoma in colorectal adenomas assessed by size and site. Int J Colorectal Dis 12(5): 267-71.

O'Leary, B. A., Olynyk, J. K., Neville, A. M. and Platell, C. F. *(2004)*. Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy. J Gastroenterol Hepatol 19(1): 38-47.

Orbell, S., Crombie, I., Robertson, A., Johnston, G. and Kenicer, M. *(1995)*. Assessing the effectiveness of a screening campaign: who is missed by 80% cervical screening coverage? J R Soc Med 88(7): 389-94.

Ott, D. J. *(2000)*. Accuracy of double-contrast barium enema in diagnosing colorectal polyps and cancer. Semin Roentgenol 35(4): 333-41.

Ott, D. J., Ablin, D. S., Gelfand, D. W. and Meschan, I. *(1983)*. Predictive value of a diagnosis of colonic polyp on the double-contrast barium enema. Gastrointest Radiol 8(1): 75-80.

Painter, J., Saunders, D. B., Bell, G. D., Williams, C. B., Pitt, R. and Bladen, J. *(1999)*. Depth of insertion at flexible sigmoidoscopy: implications for colorectal cancer screening and instrument design. Endoscopy 31(3): 227-31.

Palitz, A. M., Selby, J. V., Grossman, S., Finkler, L. J., Bevc, M., Kehr, C., *et al. (1997)*. The Colon Cancer Prevention Program (CoCaP): rationale, implementation, and preliminary results. HMO Pract 11(1): 5-12.

Pignone, M., Campbell, M. K., Carr, C. and Phillips, C. *(2001)*. Meta-analysis of dietary restriction during fecal occult blood testing. Eff Clin Pract. 4: 150-6.

Pignone, M., Saha, S., Hoerger, T. and Mandelblatt, J. *(2002)*. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 137(2): 96-104.

Potter, J. D. and Hunter, D. *(2002)*. Colorectal cancer. In: Adami, H.-O., Hunter, D., Trichopoulos, D. (eds) Textbook of cancer epidemiology. Oxford, Oxford University Press, pp 188-211.

Powe, B. D., Finnie, R. and Ko, J. *(2006)*. Enhancing knowledge of colorectal cancer among African Americans: why are we waiting until age 50? Gastroenterol Nurs 29(1): 42-9.

Rakowski, W., Clark, M. A., Truchil, R., Schneider, K. and Meersman, S. *(2005)*. Smoking status and mammography among women aged 50-75 in the 2002 behavioral risk factor surveillance system. Women Health 41(4): 1-21.

Rasmussen, M., Kronborg, O., Fenger, C. and Jorgensen, O. D. *(1999)*. Possible advantages and drawbacks of adding flexible sigmoidoscopy to hemoccult-II in screening for colorectal cancer. A randomized study. Scand J Gastroenterol 34(1): 73-8.

Richardson, A. *(2001)*. Screening and the number needed to treat. J Med Screen 8(3): 125-7.

Robinson, M. H., Berry, D. P., Vellacott, K. D., Moshakis, V. and Hardcastle, J. D. *(1993)*. Screening for colorectal cancer. Lancet 342(8865): 241.

Rothman, K. J. and Greenland, S. *(1998)*. Precision and validity in epidemiologic studies. In: Modern Epidemiology, second edition. Philadelphia, Lippincott-Raven, pp 115-134.

Sandblom, G., Varenhorst, E., Lofman, O., Rosell, J. and Carlsson, P. *(2004)*. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. Eur Urol 46(6): 717-23; discussion 724.

Santavirta, J. *(2002)*. Screening sigmoidoscopy in persons aged 60 years. Colorectal Dis 4(3): 184-188.

Scholefield, J. H., Moss, S., Sufi, F., Mangham, C. M. and Hardcastle, J. D. *(2002)*. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 50(6): 840-4.

Schroy III, P. C. and Heeren, T. C. *(2005)*. Patient perceptions of stool-based DNA testing for colorectal cancer screening. Am J Prev Med 28(2): 208-14.

Seeff, L. C., Nadel, M. R., Klabunde, C. N., Thompson, T., Shapiro, J. A., Vernon, S. W., *et al. (2004)*. Patterns and predictors of colorectal cancer test use in the adult U.S. population. Cancer 100(10): 2093-103.

Segnan, N. *(1997)*. Socioeconomic status and cancer screening. IARC Sci Publ(138): 369-76.

Segnan, N., Senore, C., Andreoni, B., Arrigoni, A., Bisanti, L., Cardelli, A., *et al. (2005)*. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. J Natl Cancer Inst 97(5): 347-57.

Segnan, N., Senore, C., Andreoni, B., Aste, H., Bonelli, L., Crosta, C., *et al. (2002)*. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy"--SCORE. J Natl Cancer Inst 94(23): 1763-72.

Selby, J. V., Friedman, G. D., Quesenberry, C. P., Jr. and Weiss, N. S. *(1992)*. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 326(10): 653-7.

Sennfalt, K., Sandblom, G., Carlsson, P. and Varenhorst, E. *(2004)*. Costs and effects of prostate cancer screening in Sweden--a 15-year follow-up of a randomized trial. Scand J Urol Nephrol 38(4): 291-8.

Seow, A., Huang, J. and Straughan, P. T. *(2000)*. Effects of social support, regular physician and health-related attitudes on cervical cancer screening in an Asian population. Cancer Causes Control 11(3): 223-30.

Shapiro, J. A., Seeff, L. C. and Nadel, M. R. *(2001)*. Colorectal cancer-screening tests and associated health behaviors. Am J Prev Med. 21: 132-7.

Shaw, C., Blakely, T., Sarfati, D., Fawcett, J. and Peace, J. *(2006)*. Trends in colorectal cancer mortality by ethnicity and socio-economic position in New Zealand, 1981-99: one country, many stories. Aust N Z J Public Health 30(1): 64-70.

Slattery, M. L., Kinney, A. Y. and Levin, T. R. *(2004)*. Factors associated with colorectal cancer screening in a population-based study: the impact of gender, health care source, and time. Prev Med 38(3): 276-83.

Slattery, M. L., Robison, L. M., Schuman, K. L., French, T. K., Abbott, T. M., Overall, J. C. Jr., *et al. (1989)*. Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. JAMA 261(11): 1593-8.

Smith, A., Young, G. P., Cole, S. R. and Bampton, P. *(2006)*. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. Cancer 107(9): 2152-9.

Smith, G. A. and O'Dwyer, P. J. *(2001)*. Sensitivity of double contrast barium enema and colonoscopy for the detection of colorectal neoplasms. Surg Endosc 15(7): 649-52.

Smith, R. A. and Haynes, S. *(1992)*. Barriers to screening for breast cancer. Cancer 69(7 Suppl): 1968-78.

Smith, R. A., von Eschenbach, A. C., Wender, R., Levin, B., Byers, T., Rothenberger, D., *et al. (2001)*. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001--testing for early lung cancer detection. CA Cancer J Clin 51(1): 38-75; quiz 77-80.

Sorlie, P. D., Backlund, E. and Keller, J. B. *(1995)*. US mortality by economic, demographic, and social characteristics: the National Longitudinal Mortality Study. Am J Public Health 85(7): 949-56.

Starkey, B. J. *(2002)*. Screening for colorectal cancer. Ann Clin Biochem 39(Pt 4): 351-65.

Statistics Sweden (2000). Name statistics [cited during year 2000]. Örebro, Sweden. Available from: http://www.scb.se/templates/Product____30909.asp

Statistics Sweden (2002). A new Total Population Register system; more possibilities and better quality. Örebro, Sweden: Serial no. 2002:2.

Statistics Sweden (2004a). Register of Education [cited 2006 April]. Örebro, Sweden. Available from: http://www.scb.se/statistik/UF/UF0506/Produktbeskrivning_short_English_UF0506_20040101r.doc

Statistics Sweden (2004b). Multi-Generation Register [cited 2006 April]. Örebro, Sweden. Available from: http://www.scb.se/statistik/_publikationer/OV9999_2004A01_BR_BE96ST0502.pdf

Statistics Sweden (SCB) (2005). Population statistics. Population in Sweden 1 November by sex and year. Year 2005. Örebro, Sweden.

Statistics Sweden (2006a). Register of Income and Wealth [cited 2006 April]. Örebro, Sweden. Available from: http://www.scb.se/templates/Product____116008.asp

Statistics Sweden (2006b). Geografidatabas. In: SCB-DATA för FORSKNING, pp 50-52. (In Swedish). Stockholm and Örebro, Sweden. Available from: http://www.scb.se/Grupp/Omscb/_Dokument/SCB-data%20för%20forskning.pdf

Stenbeck, M., Rosen, M. and Sparen, P. *(1999)*. Causes of increasing cancer prevalence in Sweden. Lancet 354(9184): 1093-4.

Stenvall, H., Wikström, I., Backlund, I. and Wilander, E. *(2007)*. Accuracy of HPV testing of vaginal smear obtained with a novel self-sampling device. Acta Obstet Gynecol Scand 86(1): 16-21.

Stewart, B. T., Keck, J. O., Duncan, A. V., Santamaria, N. M. and Allen, P. *(1999)*. Difficult or incomplete flexible sigmoidoscopy: implications for a screening programme. Aust N Z J Surg 69(1): 19-21.

Subramanian, S., Klosterman, M., Amonkar, M. M. and Hunt, T. L. *(2004)*. Adherence with colorectal cancer screening guidelines: a review. Prev Med 38(5): 536-50.

Sung, J. J., Chan, F. K., Leung, W. K., Wu, J. C., Lau, J. Y., Ching, J., *et al. (2003)*. Screening for colorectal cancer in Chinese: comparison of fecal occult blood test, flexible sigmoidoscopy, and colonoscopy. Gastroenterology 124(3): 608-14.

Sutton, S., Wardle, J., Taylor, T., McCaffery, K., Williamson, S., Edwards, R., *et al. (2000)*. Predictors of attendance in the United Kingdom flexible sigmoidoscopy screening trial. J Med Screen 7(2): 99-104.

Swan, J., Breen, N., Coates, R. J., Rimer, B. K. and Lee, N. C. *(2003)*. Progress in cancer screening practices in the United States: results from the 2000 National Health Interview Survey. Cancer 97(6): 1528-40.

Swaroop, V. S. and Larson, M. V. *(2002)*. Colonoscopy as a screening test for colorectal cancer in average-risk individuals. Mayo Clin Proc 77(9): 951-6.

Swedish Council on Technology Assessment in Health Care (SBU) (2001).
SBU Alert-report, Screening for colorectal cancer [cited 2007 April]. Stockholm, Sweden. Available from: http://www.sbu.se/Filer/Content0/publikationer/3/Screening_colorectal.pdf

Swedish Council on Technology Assessment in Health Care (2002).
SBU Alert-report, Computed tomography in screening for lung cancer [cited 2007 April]. Stockholm, Sweden. Available from: http://www.sbu.se/Filer/Content0/publikationer/3/CT.pdf

Taplin, S., Anderman, C. and Grothaus, L. *(1989)*. Breast cancer risk and participation in mammographic screening. Am J Public Health 79(11): 1494-8.

Taylor, K. L., Shelby, R., Gelmann, E. and McGuire, C. *(2004)*. Quality of life and trial adherence among participants in the prostate, lung, colorectal, and ovarian cancer screening trial. J Natl Cancer Inst 96(14): 1083-94.

The Swedish Organised Service Screening Evaluation Group (2006a). Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. Cancer Epidemiol Biomarkers Prev 15(1): 45-51.

The Swedish Organised Service Screening Evaluation Group (2006b). Reduction in breast cancer mortality from the organised service screening with mammography: 2. Validation with alternative analytic methods. Cancer Epidemiol Biomarkers Prev 15(1): 52-6.

Thiis-Evensen, E., Hoff, G. S., Sauar, J., Langmark, F., Majak, B. M. and Vatn, M. H. *(1999)*. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol 34(4): 414-20.

Thompson, M. R., Steele, R. J. and Atkin, W. S. *(2006)*. Effective screening for bowel cancer: a United kingdom perspective. Dis Colon Rectum 49(6): 895-908.

Turner, B. J., Weiner, M., Yang, C. and TenHave, T. *(2004)*. Predicting adherence to colonoscopy or flexible sigmoidoscopy on the basis of physician appointment-keeping behavior. Ann Intern Med 140(7): 528-32.

Turrell, G., Patterson, C., Oldenburg, B., Gould, T. and Roy, M. A. *(2003)*. The socio-economic patterning of survey participation and non-response error in a multilevel study of food purchasing behaviour: area- and individual-level characteristics. Public Health Nutr 6(2): 181-9.

UK Flexible Sigmoidoscopy Screening Trial Investigators (2002). Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet 359(9314): 1291-300.

Vernon, S. W. *(1997)*. Participation in colorectal cancer screening: a review. J Natl Cancer Inst 89(19): 1406-22.

Vogelstein, B., Fearon, E. R., Hamilton, S. R., Kern, S. E., Preisinger, A. C., Leppert, M., *et al. (1988)*. Genetic alterations during colorectal-tumor development. N Engl J Med 319(9): 525-32.

Wacholder, S. *(1986)*. Binomial regression in GLIM: estimating risk ratios and risk differences. Am J Epidemiol 123(1): 174-84.

Wardle, J., Sutton, S., Williamson, S., Taylor, T., McCaffery, K., Cuzick, J., *et al. (2000)*. Psychosocial influences on older adults' interest in participating in bowel cancer screening. Prev Med 31(4): 323-34.

Waye, J. D. *(1986)*. Colon polyps: problems, promises, prospects. Am J Gastroenterol 81(2): 101-3.

Wee, C. C., McCarthy, E. P. and Phillips, R. S. *(2005)*. Factors associated with colon cancer screening: the role of patient factors and physician counseling. Prev Med 41(1): 23-9.

Weishaupt, D., Patak, M. A., Froehlich, J., Ruehm, S. G. and Debatin, J. F. *(1999)*. Faecal tagging to avoid colonic cleansing before MRI colonography. Lancet 354(9181): 835-6.

Weissfeld, J. L., Ling, B. S., Schoen, R. E., Bresalier, R. S., Riley, T. and Prorok, P. C. *(2002)*. Adherence to repeat screening flexible sigmoidoscopy in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer 94(10): 2569-76.

Wen, L., Badgett, R. and Cornell, J. *(2005)*. Number needed to treat: a descriptor for weighing therapeutic options. Am J Health Syst Pharm 62(19): 2031-6.

Wilson, J. M. G., Jungner G. *(1968)*. Principles and practice of screening for disease. World Health Organization, Geneva.

Winawer, S., Fletcher, R., Rex, D., Bond, J., Burt, R., Ferrucci, J., *et al. (2003)*. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology 124(2): 544-60.

Winawer, S. J., Zauber, A. G., Ho, M. N., O'Brien, M. J., Gottlieb, L. S., Sternberg, S. S., *et al. (1993)*. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 329(27): 1977-81.

Wong, N. Y., Nenny, S., Guy, R. J. and Seow-Choen, F. *(2002)*. Adults in a high-risk area are unaware of the importance of colorectal cancer: a telephone and mail survey. Dis Colon Rectum 45(7): 946-50; quiz 951-4.

Yeazel, M. W., Church, T. R., Jones, R. M., Kochevar, L. K., Watt, G. D., Cordes, J. E., *et al. (2004)*. Colorectal cancer screening adherence in a general population. Cancer Epidemiol Biomarkers Prev 13(4): 654-7.

Yee, J., Akerkar, G. A., Hung, R. K., Steinauer-Gebauer, A. M., Wall, S. D. and McQuaid, K. R. *(2001)*. Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. Radiology 219(3): 685-92.

Zuber, T. J. *(2001)*. Flexible sigmoidoscopy. Am Fam Physician 63(7): 1375-80, 1383-8.

APPENDIX

Invitation to group 1 (called up by nurse)

Hälsoundersökning riktad mot tjocktarmstumör

Härmed inbjudes Du att delta i följande studie

Cancer i tjock- och ändtarmen är den vanligaste cancerformen i magtarmkanalen med 4 700 nya fall per år i Sverige. Patienter med tidigare stadier av cancer har bättre överlevnad än fall upptäckta i mer avancerat stadium. Om sjukdomen upptäckes tidigt finns effektiv behandling. Polyper i tarmen kan utgöra förstadier till cancer och om de avlägsnas minskas risken för senare tumörutveckling.

Flera stora medicinska undersökningar som slutförts under de senaste tre åren talar för att man kan sänka sjuklighet och dödlighet i tjocktarmstumör genom att göra hälsoundersökningar. En metodik som visat lovande resultat är att man med ett böjligt instrument undersöker de nedersta 60 cm av tjocktarmen. Det är inom detta område som det är vanligast att tjocktarmstumörer finns. Undersökningsresultaten har varit så lovande att flera betydelsefulla medicinska sammanslutningar och många läkare rekommenderar att metoden ska införas som rutin.

Inbjudan att delta i en svensk undersökning

Det finns emellertid en del faktorer som närmare måste utredas. T ex vet vi ännu inte hur mycket sjuklighet och dödlighet kan sänkas, det finns fortfarande inte helt klarlagt hur de undersökta upplever hälsokontrollen, det är osäkert hur mycket resurser som krävs för att undersöka alla svenskar i vissa åldrar. Med stöd av Riksföreningen mot Cancer har vi börjat en undersökning för att försöka lösa några av dessa frågor, framför allt hur undersökningen upplevs av de inbjudna och hur stor resursåtgången är.

Hur går undersökningen till?

Du tillhör en grupp av män och kvinnor i 55-65-årsåldern som slumpvis utvalts att inbjudas till undersökningen. Sammanlagt har ungefär 2 000 personer inbjudits i Uppsala och Malmöhus län. Du erbjuds att genomgå en hälsoundersökning där vi undersöker de sista 60 cm av tjocktarmen precis på samma sätt som man skulle göra i en stor hälsoundersökning riktad till hela befolkningen i Din åldersgrupp. Själva hälsoundersökningen innehåller inte några extra moment, provtagningar eller dylikt utöver vad en tilltänkt rutinmässig hälsokontroll skulle göra. Undersökningen kan av vissa personer upplevas obehaglig och smärtsam. Om Du upplever detta kommer smärtstillande medicin att ges.

Ett avföringsprov kommer att sparas för senare analys.

Emellertid kommer vi att be Dig om hjälp med att fylla i två stycken frågeformulär. Ett frågeformulär bifogas detta inbjudningsbrev. Med hjälp av detta frågeformulär vill vi utröna om det finns några riskfaktorer vad avser tidigare sjukdomar, medicinering och livsstilsmönster för godartade och elakartade tumörer i tjocktarmen. Om vi finner några sådana riskfaktorer kan dessa ligga till grund för förebyggande verksamhet. Ta med Ditt frågeformulär när Du kommer för undersökningen. När Du genomfört själva undersökningen kommer vi att be Dig att fylla i ännu ett mycket kort frågeformulär där Du talar om hur Du upplevde undersökningen och där vi också frågar hur Du rest till och från undersökningen och hur mycket ledigt från arbetet Du har tvingats ta.

Efter undersökningen

Vad händer efter undersökningen? Om undersökningsfyndet är helt normalt behöver Du inte genomgå en ny undersökning på många år. Många av de uppgifter vi har idag talar för att en sådan här undersökning kan ha en förebyggande effekt ända uppemot tio år framåt. Om vi hittar en tjocktarmstumör av något slag (godartad eller elakartad) så erbjuder vi Dig naturligtvis behandling. De flesta kommer att ha helt normalt fynd. Det näst vanligaste är att man hittar polyper i tarmen som nästan alltid kan avlägsnas via ett böjligt fiberoptiskt instrument och således inte behöver opereras bort med något bukingrepp. Om en tjocktarmstumör hittas, så är naturligtvis målsättningen att operera den så snart som möjligt för att ge bästa möjliga chans till bot.

Deltagande i undersökningen är frivilligt

Deltagande i undersökningen är naturligtvis helt frivilligt och utan kostnad. Däremot måste Du stå för resekostnaden själv. All personal som hanterar inbjudan, enkätsvaren, deltar vid undersökningen och uppföljningen o s v har full tystnadsplikt precis som i sjukvården i övrigt. De uppgifter Du lämnar i enkäten kommer att registreras på datamedium för statistikbearbetning. All redovisning av resultat sker i form av statistiska tabeller och resultat där en enskild persons svar inte kan utläsas.

Syster Annika (adress och telefonnummer nedan) kommer att ta kontakt med Dig inom två veckor för att boka tid för undersökning. Om Du har frågor om undersökningen kan Du själv ta kontakt med henne.

Syster Annika	Telefon: 018 - 66 38 96
Kirurgiska kliniken	Måndagar, torsdagar och fredagar kl 13.00 - 14.00
Akademiska sjukhuset	Tisdagar kl 8.30 - 11.30

Lars Holmberg
Docent, överläkare
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205 02 Malmö

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Kirurgiska kliniken
Akademiska sjukhuset
751 85 Uppsala

Invitation to group 2 (asked to call themselves)

Hälsoundersökning riktad mot tjocktarmstumör

Härmed inbjudes Du att delta i följande studie

Cancer i tjock- och ändtarmen är den vanligaste cancerformen i magtarmkanalen med 4 700 nya fall per år i Sverige. Patienter med tidigare stadier av cancer har bättre överlevnad än fall upptäckta i mer avancerat stadium. Om sjukdomen upptäckes tidigt finns effektiv behandling. Polyper i tarmen kan utgöra förstadier till cancer och om de avlägsnas minskas risken för senare tumörutveckling.

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Inbjudan att delta i en svensk undersökning

Det finns emellertid en del faktorer som närmare måste utredas. T ex vet vi ännu inte hur mycket sjuklighet och dödlighet kan sänkas, det finns fortfarande inte helt klarlagt hur de undersökta upplever hälsokontrollen, det är osäkert hur mycket resurser som krävs för att undersöka alla svenskar i vissa åldrar. Med stöd av Riksföreningen mot Cancer har vi börjat en undersökning för att försöka lösa några av dessa frågor, framför allt hur undersökningen upplevs av de inbjudna och hur stor resursåtgången är.

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Emellertid kommer vi att be Dig om hjälp med att fylla i två stycken frågeformulär. Ett frågeformulär bifogas detta inbjudningsbrev. Med hjälp av detta frågeformulär vill vi utröna om det finns några riskfaktorer vad avser tidigare sjukdomar, medicinering och livsstilsmönster för godartade och elakartade tumörer i tjocktarmen. Om vi finner några sådana riskfaktorer kan dessa ligga till grund för förebyggande verksamhet. Ta med Ditt frågeformulär när Du kommer för undersökningen. När Du genomfört själva undersökningen kommer vi att be Dig att fylla i ännu ett mycket kort frågeformulär där Du talar om hur Du upplevde undersökningen och där vi också frågar hur Du rest till och från undersökningen och hur mycket ledigt från arbetet Du har tvingats ta.

Efter undersökningen

Vad händer efter undersökningen? Om undersökningsfyndet är helt normalt behöver Du inte genomgå en ny undersökning på många år. Många av de uppgifter vi har idag talar för att en sådan här undersökning kan ha en förebyggande effekt ända uppemot tio år framåt. Om vi hittar en tjocktarmstumör av något slag (godartad eller elakartad) så erbjuder vi Dig naturligtvis behandling. De flesta kommer att ha helt normalt fynd. Det näst vanligaste är att man hittar polyper i tarmen som nästan alltid kan avlägsnas via ett böjligt fiberoptiskt instrument och således inte behöver opereras bort med något bukingrepp. Om en tjocktarmstumör hittas, så är naturligtvis målsättningen att operera den så snart som möjligt för att ge bästa möjliga chans till bot.

Deltagande i undersökningen är frivilligt

Deltagande i undersökningen är naturligtvis helt frivilligt och utan kostnad. Däremot måste Du stå för resekostnaden själv. All personal som hanterar inbjudan, enkätsvaren, deltar vid undersökningen och uppföljningen o s v har full tystnadsplikt precis som i sjukvården i övrigt. De uppgifter Du lämnar i enkäten kommer att registreras på datamedium för statistikbearbetning. All redovisning av resultat sker i form av statistiska tabeller och resultat där en enskild persons svar inte kan utläsas.

Du som vill deltaga skall kontakta syster Annika (adress och telefonnummer nedan) för att boka tid för undersökning. Hon kan också svara på Dina eventuella frågor angående undersökningen.

Syster Annika	Telefon: 018 - 66 38 96
Kirurgiska kliniken	Måndagar, torsdagar och fredagar kl 13.00 - 14.00
Akademiska sjukhuset	Tisdagar kl 8.30 - 11.30

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Questionnaire after the sigmoidoscopy

I denna enkät önskar vi att Du svarar på några frågor om den undersökning Du just gått igenom. Vissa frågor besvaras med ett kryss i den ruta som bäst beskriver just Din situation. Andra frågor besvaras genom att markera med ett kryss på en horisontell linje, detta för att Du lättare skall kunna gradera Din uppfattning om undersökningen. Exempelvis om Du i fråga 1 tyckte att det var mer positivt att få kallelsen än Du upplevde Dig illa berörd, så markerar Du med ett kryss mer till vänster på linjen.

Tack för Din medverkan!

1. Hur upplevde Du det att få kallelse till denna undersökning?

det var positivt ⊢——————————————————⊣ blev illa berörd

2. Tyckte Du, då Du fick kallelsen, att den tillräckligt förklarade vad tarmundersökningen innebar?

☐ ja ☐ nej

3. Hur tycker Du att undersökningen överensstämde med den föreställning Du gjorde Dig?

helt ⊢——————————————————⊣ inte alls

4. Hur lång tid tog det Dig att komma hit till undersökningen?

☐ 15 min. ☐ 30 min. ☐ 45 min. ☐ 1 timme ☐ >1 timme

5. Hur kom Du hit?

☐ promenad ☐ cykel ☐ buss ☐ egen bil ☐ annat: .....

6. Har Du tagit ledigt från Ditt arbete för att komma hit?

☐ nej ☐ ja, 1/2 dag ☐ ja, 1 dag ☐ ja, > 1 dag

7. Har Du tagit ledigt från Ditt arbete för att genomföra förberedelserna (fasta, lavemang och dylikt)?

☐ nej ☐ ja, 1/2 dag ☐ ja, 1 dag ☐ ja, > 1 dag

8. Kommer Du att ta extra ledigt i morgon också?

☐ ja ☐ nej

9. Har Du frikort?

☐ ja ☐ nej

Om själva undersökningen:

10. Hur upplevde Du förberedelserna inför undersökningen?

det var positivt ⊢——————————————⊣ blev illa berörd

11. Var Du nervös innan undersökningen?

inte alls ⊢——————————————⊣ mycket

12. Var Du nervös under själva undersökningen?

inte alls ⊢——————————————⊣ mycket

13. Var Du rädd att man skulle finna en tumör vid undersökningen?

inte alls ⊢——————————————⊣ mycket

14. Tyckte Du att undersökningen gjorde ont?

inte alls ⊢——————————————⊣ mycket

15. Kände Du Dig uppspänd i tarmen?

inte alls ⊢——————————————⊣ mycket

16. Kände Du Dig utlämnad?

inte alls ⊢——————————————⊣ mycket

17. Upplevde Du att undersökningen tog lång tid?

inte alls ⊢——————————————⊣ mycket

18. Tyckte Du att undersökningen var obehaglig i övrigt?

inte alls ⊢——————————————⊣ mycket

Egen kommentar: .....

19. Vi planerar inte att kalla Dig till en ytterligare tarmundersökning, men skulle Du kunna tänka Dig att genomgå undersökningen igen om den skulle visa sig kunna sänka risken för sjuklighet i tjocktarmstumör?

☐ nej ☐ ja, om 2 år ☐ ja, om 5 år ☐ ja, om 10 år

20. Skulle Du rekommendera en vän att genomgå samma undersökning?

inte alls ⊢——————————————————⊣ mycket

Egen kommentar: .....

Sigmoidoscopy protocol filled out by the endoscopist

PROTOKOLL FÖR SIGMOIDEOSKOPI

Datum: _____

Skopist: _____

Fullständig undersökning ☐ ja ☐ nej

Hur långt _____ cm Läge i tarmen: _____

Hur bedömde Du patientens grad av besvär under undersökningen?

inga alls ⊢——————————————————⊣ mycket besvär

Anledning till avbruten undersökning (flera alternativ tillåtna)

- ☐ Otillräckligt rengjord tarm
- ☐ Smärta
- ☐ Tidigare bukoperation
- ☐ Annat _____

Fynd

	Hyperplastiska polyper		Neoplastiska polyper	
☐ Negativ				
☐ Hyperplastiska polyper, antal _____	cm från anus	mm i diam.	cm från anus	mm i diam.
☐ Neoplastiska polyper, antal _____	1. _____	_____	1. _____	_____
☐ Cancer _____ cm från, anus	2. _____	_____	2. _____	_____
☐ Divertiklar	3. _____	_____	3. _____	_____
☐ Obstruktion	4. _____	_____	4. _____	_____
☐ IBD	5. _____	_____	5. _____	_____
☐ Annat _____				

Bedömbarhet i relation till tarmrengöring ☐ bra
☐ acceptabel
☐ dålig

Tid för skopin _____ minuter

Komplikationer ☐ nej ☐ ja _____

Remiss för colonoskopi ☐ ja ☐ nej