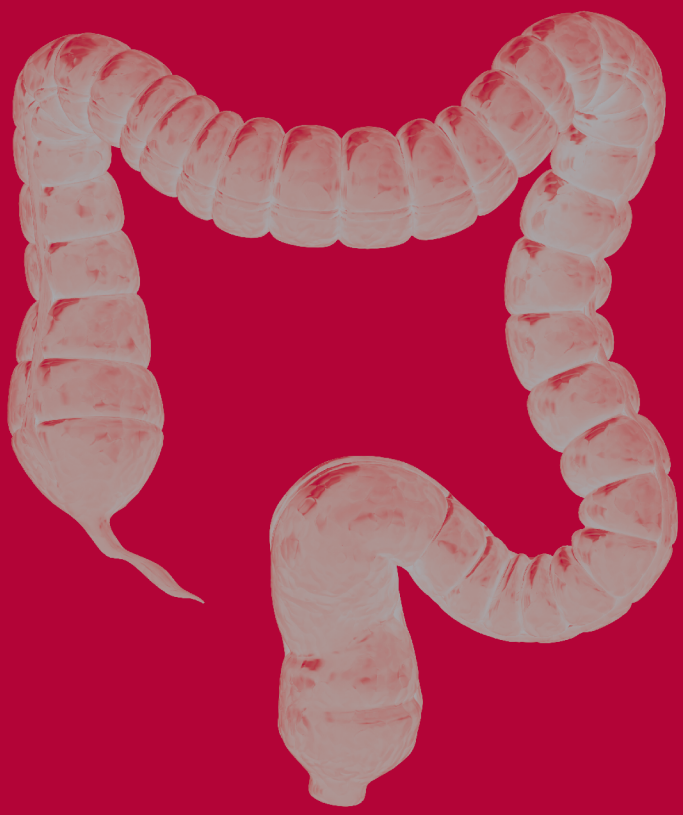
POPULATION-BASED COLORECTAL CANCER SCREENING

BY COLONOSCOPY OR CT COLONOGRAPHY



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Population-based Colorectal Cancer Screening by Colonoscopy or CT colonography

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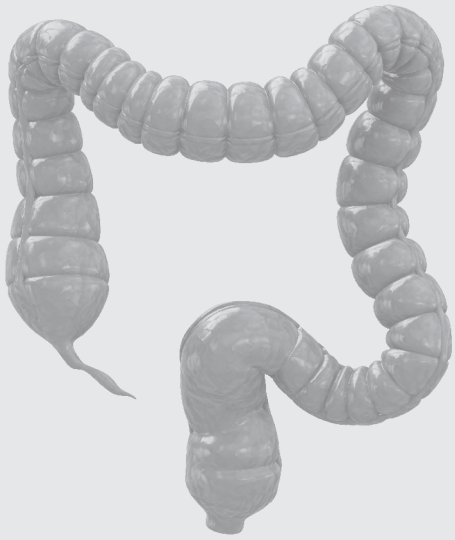
CHAPTER 1

General introduction and outline of the thesis



E. M. Stoop

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

In 1968 at request of the World Health Organization (WHO), Wilson and Jungner defined 10 criteria for informed population-based screening.(1) In subsequent years, these criteria have been reevaluated and revised several times. In their most recent version, they can be summarized as follows: *screening has to aim at an important health issue,* and *it has to result in substantial health gain or lead to other healthcare benefits*. Besides, *the method of screening must be reliable and valid*. Finally, *participation in screening has to be based on informed choice and must be completely voluntarily.*

Colorectal cancer can be considered *an important healthcare problem*. Colorectal cancer is the third most common cancer worldwide and the second leading cause of cancer-related mortality.(2) The lifetime risk in the US population is 5%-6% without screening(3), which is similar in the Netherlands.(4) More than 400 000 persons are diagnosed with colorectal cancer each year in Europe.(5) The prognosis of CRC depends on the stage at the time of diagnosis; in the Netherlands, the 5-year-survival rate of stage I CRC is 94% compared to 8% for stage IV.(4) Several studies have shown that colorectal cancer screening is effective in the average risk population.(6-8) Besides, screening for CRC is thought to be cost-effective.(9) Screening can be performed with a range of different methods and strategies. Available methods for colorectal-cancer screening fall into two broad categories; stool tests (guaiac fecal occult blood test (gFOBT), fecal immunochemical test (FIT) and DNA tests) and structural examinations (flexible sigmoidoscopy, colonoscopy, and computed tomographic colonography).

Stool testing is a non-invasive and widely accepted screening method. One of those stool-based tests is guaiac-based gFOBT, which is primarily used for early detection of CRC.(6) This test reacts to the presence of heme and is used to screen for the presence of occult blood in stool. The most common and traditionally used gFOBTs are the guaiac-impregnated Hemoccult II and the more sensitive Hemoccult II SENSA.(10, 11) A disadvantage is that the gFOBT also detects heme from upper gastrointestinal bleedings causing false-positive test results. (12) A newer stool-based test is the FIT. This test reacts to the presence of globin instead of heme, which is one of the reasons that this is a more sensitive test. Due to the higher sensitivity, improved detection rate of advanced neoplasia, the possibility for automated reading, quantitative which allows for determination of a cut-off for colonoscopy referral, and substantially higher uptake due to the ease of the test, this test is gaining more and more acceptance.(13-18) FIT has another important advantage over gFOBT besides the higher sensitivity, which is the easier stool collection.(14, 15, 19) With the quantitative FIT, the cut-off value can be changed in order to optimize sensitivity and specificity of the test. This cut-off level is based on the correlation between the amount of fecal hemoglobin

detected by FIT and the severity of disease.(20, 21) Besides, this cut-off value can be varied depending on colonoscopy resources available and intended detection rate in the screened population.(17)

Stool-based DNA marker tests are designed to trace gene mutations in exfoliated epithelial cells that are secreted into the feces. This method is based on findings that specific mutations are associated with the development of CRC (such as K-ras and p53). (22)

Two full-colon structural exams for CRC screening are colonoscopy and CT colonography. These two examinations are subject of this thesis. They are both characterized by a presumed high sensitivity for advanced neoplasia, but also by the need for bowel preparation, higher burden, the need to attend an outpatient clinic, and overall higher costs.

Colonoscopy is widely accepted as the reference standard for detection of adenomas and CRC. It is an endoscopic technique to visualize the entire colon and to detect and immediately remove neoplastic lesions. Tandem-colonoscopy studies showed that the sensitivity is between 90%-98% for large adenomas (>10mm) and around 87% for 6-9mm adenomas.(23) Colonoscopy can be repeated with long intervals since the risk of developing CRC after a negative colonoscopy remains low for more than 10 years. (24) Disadvantages are the need for full bowel cleansing, burden of the procedure, and the complication rate of 0.1%-0.3%, including post-polypectomy bleeding and perforation(25, 26) Colonoscopy can be used as a primary screening method, but is also used as a secondary screening method for screenees with a positive stool-based test, a positive sigmoidoscopy or CTC. To date, no randomized controlled trials have been performed to assess the efficacy of colonoscopy in screening. However, since 2010, the Nordic-European Initiative on Colorectal Cancer (NordICC) trial was initiated. This is a multicentre collaborative study in which the Nordic countries, Poland and the Netherlands perform screening colonoscopies. The colonoscopy arm of the study forming the basis for this thesis (COCOS trial) is part of the NordICC trial. Final results are expected in 2026.

CT Colonography is a minimally invasive procedure to visualize the entire colon, using a small-caliber flexible rectal catheter for colonic distension using CO2 insufflation. Its estimated sensitivity in detecting adenomas ≥10mm in a screening population is 88%, versus 79% for 6-9mm adenomas.(27) Advantages of CT colonography are the use of limited bowel preparation and the low risk of complications.(28) Disadvantages are the exposure to ionizing radiation (although low dose protocols are now available) and the need for subsequent colonoscopy if significant lesions are detected. There is still no consensus on the optimal referral criteria for colonoscopy. In most countries, participants with one or more polyps of 6 mm or larger are referred to colonoscopy. (29, 30)

Both screening methods can be characterized as *reliable and valid* when looking at sensitivity and specificity.

The COCOS (COlonoscopy or COlonography for Screening) trial was a randomized controlled trial comparing colonoscopy and CT Colonography in a population-based screening program in the Netherlands. (31) **The general aim** of the trial was to compare participation, diagnostic yield, burden and time-investment between colonoscopy and CT colonography in screening. Besides, we aimed to calculate unit-costs for both screening methods.

In **chapter 2**, participation and diagnostic yield of both methods are described. Several trials already reported on participation rates in colonoscopy screening. In an Italian trial, a participation rate of 10% was found. (32) The annual participation rates for the age group 55-69 years in the screening program in Germany, our neighbouring country, were 3% for men and 4% for women. (33) To our knowledge, only one previous RCT reported on participation rates in CTC screening (participation rate of 18 percent). (34) Diagnostic yield of colonoscopy and CT Colonography has been investigated in several other studies. (35-37) However, to our knowledge, only one other RCT comparing participation and diagnostic yield of both methods has been published to date. (34)

Participation rate and diagnostic yield are the two main parameters that determine whether population-based screening is effective in gaining health in the general population. Because of the fact that participation in screening is completely voluntarily and initial participation can be influenced by expected burden of the procedure, expected and perceived burden were examined in our RCT. It was expected that invitees would anticipate colonoscopy to be more burdensome than CT colongraphy, among others because of the extensive bowel preparation. On the other hand, participants could anticipate CT colonography as more burdensome compared to colonoscopy because of diarrhea after the examination. To our knowledge no studies have been published comparing both the expected and perceived burden of colonoscopy and CT-colonography. Therefore, in **chapter 3**, a comparison was made between expected- and perceived burden of colonoscopy versus CT colonography in screening as well as participants' willingness to return in future screening rounds.

Not only effectiveness in gaining health, but also cost-effectiveness is an important issue in population screening. Several cost-effectiveness analyses have been performed for colonoscopy in screening. (38-40) However, in these analyses colonoscopy costs were generally based on clinical reimbursements, based on clinical patient care. These estimates may not be representative of the actual costs for screening colonoscopies and are most likely overestimated. One can presume that costs for one colonoscopy in a dedicated high throughput screening setting are lower than the costs for one regular colonoscopy in a clinical setting. In **chapter 4**, costs per colonoscopy in a

dedicated screening setting were calculated and in addition, the costs for alternative implementation scenarios in screening were estimated. We also calculated the actual unit costs for CT colonography screening and described these costs separately. (41)

In population-based screening, screenees have to be informed about the risks and benefits of the concerning screening method in order to enable informed decision making. In other words, *participation in screening has to be based on informed choice and must be completely voluntarily.*

Besides, information on a person's medical history and medication use should be obtained to anticipate on possible risks during the screening procedure. Most hospitals in the Netherlands invite patients at the outpatient clinic prior to colonoscopy. Although this is working well in daily clinical practice, it may overload the outpatient clinic when used in screening. In **chapter 5**, two types of pre-colonoscopy consultations have been compared regarding response rate and participation rate. In order to compare a pre-colonoscopy assessment by telephone to a face-to-face consultation at the outpatient clinic, 6600 persons were randomized to one of the two groups. Besides response rate and participation, participants' satisfaction, expected and perceived burden and quality of bowel preparation were compared.

In 2013, in the Netherlands, population-based CRC screening will be initiated, using FIT as the primary screening method. The overall sensitivity for CRC and advanced neoplasia is between 61% and 91%, the overall specificity between 91% and 98%. (42) Although FIT screening is implemented in various countries worldwide, solid data evaluating FIT against colonoscopy as the reference standard are scarce as most studies to date have only performed colonoscopy in subjects with a positive FIT, but not in those with a negative FIT. Besides, when colonoscopy is only performed after a positive-FIT, undetected right-sided neoplasia by colonoscopy will result in a lower sensitivity for detecting colorectal neoplasia in FIT screening. In **chapter 6,** we aimed to estimate the sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of FIT in screening-naïve participants within a population-based colonoscopy screening trial, using colonoscopy as the primary screening method. In addition, we aimed to evaluate FIT sensitivity in detecting right-sided and left -sided advanced neoplasia.

Colonoscopy is considered the most accurate method and reference standard for the detection of colorectal neoplasia. However a substantial number of right-sided polyps might be missed during colonoscopy. The prevalence of left-sided advanced colorectal advanced neoplasia, but not right-sided advanced neoplasms, was strongly reduced within a ten-year period after colonoscopy in a German trial. (43) A Canadian study demonstrated a marked difference in the strength of the association of colonoscopy with CRC death for proximally and distally located cancers. (44) One of the reasons may be that proximal adenomas in the left colon are often flat and more difficult to

identify than pedunculated or sessile polyps.(45) In addition, distal cancers are more likely to develop through the chromosomal instability pathway with the classic slow progression of adenoma to carcinoma than proximal colon cancers. This might be an explanation why the colonoscopic detection of adenomas is better in the left colon. (45)

Proximally located serrated polyps also have a flat morphology and ambiguous color. In combination with insufficient bowel preparation of the proximal colon, there is an increased risk of not detecting these lesions during colonoscopy. Because of the fact that these serrated polyps can develop into CRC through the serrated pathway, it is important that these polyps are detected during colonoscopy. In **chapter 7** we aimed to identify different factors associated with the detection of proximal serrated polyps (PSP) during colonoscopy. Procedure-related factors such as intubation and withdrawal times but also patient-related factors such as gender, age and quality of bowel preparation were analyzed, in order to identify an association with detection of these proximal serrated polyps.

In order to improve adenoma detection, a transparent plastic cap was designed which can be attached to the tip of a colonoscope. The cap may increase colonic surface visualization by flattening the semilunar folds with the cap. In addition, a better endoscopic view can be created by keeping an appropriate distance between the tip of the colonoscope and the mucosa. A disadvantage of these caps might be that the view is blurred if the bowel preparation is poor, as fecal material can remain in the cap. A recent meta-analysis could not draw any conclusions supporting improved adenoma detection using this transparent cap.(46) In **chapter 8**, we aimed to compare adenoma detection of conventional colonoscopy with cap-assisted colonoscopy. Secondary outcomes in this study were cecal intubation time, cecal intubation rate and the degree of discomfort during colonoscopy.

Finally in **chapter 9**, the main findings of this thesis and thus the COCOS trial are summarized and discussed.

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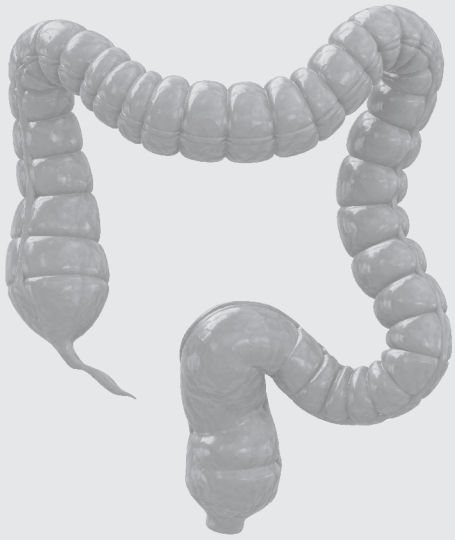
CHAPTER 2

Participation and Yield of Colonoscopy versus Non-Cathartic CT Colonography in Population-Based Colorectal Cancer Screening: a Randomized Controlled Trial



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ABSTRACT

Background: Screening for colorectal cancer is widely recommended, but the preferred strategy remains unidentified. We aimed to compare participation and diagnostic yield between screening with colonoscopy and with non-cathartic CT colonography.

Methods: Members of the general population, aged 50 to 75 years, and living in the regions of Amsterdam or Rotterdam, identified via the registries of the regional municipal administration, were randomly allocated (2:1) to be invited for primary screening for colorectal cancer by colonoscopy or by CT colonography. Randomization was done per household with a minimisation algorithm based on age, sex, and socioeconomic status. Invitations were sent between June 8, 2009, and August 16, 2010. Participants assigned to CT colonography who were found to have one or more large lesions (≥10 mm) were offered colonoscopy; those with 6–9 mm lesions were offered surveillance CT colonography. The primary outcome was the participation rate, defined as number of invitees undergoing the examination relative to the total number of invitees. Diagnostic yield was calculated as number of participants with advanced neoplasia relative to the total number of invitees. Invitees and screening centre employees were not masked to allocation. This trial is registered in the Dutch trial register, number NTR1829.

Findings: 1,276 (22%) of 5,924 colonoscopy invitees participated, compared with 982 (34%) of 2,920 CT colonography invitees (relative risk [RR] 1.56, 95% CI 1.46–1.68; p<0.0001). Of the participants in the colonoscopy group, 111 (9%) had advanced neoplasia of whom seven (<1%) had a carcinoma. Of CT colonography participants, 84 (9%) were offered colonoscopy, of whom 60 (6%) had advanced neoplasia of whom five (<1%) had a carcinoma; 82 (8%) were offered surveillance. The diagnostic yield for all advanced neoplasia was 8.7 per 100 participants for colonoscopy vs. 6.1 per 100 for CT colonography (RR 1.46, 95% CI 1.06–2.03; p=0.02) and 1.9 per 100 invitees for colonoscopy and 2.1 per 100 invitees for CT colonography (RR 0.91, 0.66–2.03; p=0.56). The diagnostic yield for advanced neoplasia of 10 mm or more was 1.5 per 100 invitees for colonoscopy and 2.0 per 100 invitees for CT colonography, respectively (RR 0.74, 95% CI 0.53–1.03; p=0.07). Serious adverse events related to the screening procedure were post-polypectomy bleedings: two in the colonoscopy group and three in the CT colonography group.

Interpretation: Participation in colorectal cancer screening with CT colonography was significantly better than with colonoscopy, but colonoscopy identified significantly more advanced neoplasia per 100 participants than did CT colonography. The diagnostic yield for advanced neoplasia per 100 invitees was similar for both strategies, indicating that both techniques can be used for population-based screening for colorectal cancer. Other factors such as cost-effectiveness and perceived burden should be taken into account when deciding which technique is preferable.

INTRODUCTION

Colorectal cancer (CRC) is the second most prevalent cause of cancer-related mortality in Europe. (1) The lifetime risk in the US population is 5–6% without screening (2), similar to that in the Netherlands. (3) The prognosis of CRC depends on the stage at the time of diagnosis; in the Netherlands, 5-year survival of patients with stage I CRC is 94% compared with 8% for stage IV. (3) In most cases, the disease develops from adenomatous polyps after a long premalignant state. Substantial evidence exists that screening reduces CRC mortality both by early detection of cancers and by endoscopic removal of adenomas. (4) Colonoscopy and CT colonography visualise the complete colon and enable early detection of advanced adenomas and CRCs. These techniques could therefore lead to a decrease of incidence of this disease. (5)

Colonoscopy is widely accepted as the reference standard for detection of adenomas and CRCs. Results from tandem-colonoscopy studies and comparative studies with CT colonography showed that the sensitivity is between 88% and 98% for large adenomas (≥10 mm) (6;7) and about 87% for 6–9 mm adenomas.(6) Colonoscopy has the advantage that adenomas can be removed directly. Additionally, colonoscopy can be repeated with long intervals because the risk of developing CRC after a negative colonoscopy remains low for more than 10 years. (8) However, the protective effect seems to be less clear for right-sided cancers and is related to the quality of the procedure. (9) Disadvantages are the need for full bowel cleansing, burden of the procedure, and the complication rate of 0.1–0.3%, such as post-polypectomy bleeding and perforation. (10;11)

CT colonography could be a valuable alternative for colonoscopy. Its estimated sensitivity in detection of large adenomas (≥10 mm) in a screening population is 88%, compared with 79% for 6–9 mm adenomas.(12) Important advantages of CT colonography are its minimally invasive nature (only a small-calibre flexible rectal catheter is needed for colonic distension), the use of limited bowel preparation (13;14), and low risk of complications.(15) Disadvantages are the exposure to ionizing radiation, although low-dose protocols are now available, and the need for subsequent colonoscopy if substantial lesions are detected.

Several studies have compared the accuracy and yield of colonoscopy and CT colonography in an average risk population. (12) However, the effectiveness of a population-based screening program does not only depend on the detection rate of the screening technique, but also on the participation rate. One could hypothesise that CT colonography will be perceived as less burdensome, leading to a higher participation in CT-based screening. The aim of this population-based randomized trial was to compare the participation and diagnostic yield of colonoscopy and non-cathartic CT colonography in average risk individuals in a population-based program of colorectal cancer screening.

METHODS

Study design and participants

This randomized controlled trial was done in the Netherlands, at the Academic Medical Centre in Amsterdam and the Erasmus University Medical Centre in Rotterdam. Individuals, not previously invited for screening for CRC, aged 50 to 75 years, and of the general Dutch population in the regions of Amsterdam and Rotterdam, were invited for CRC screening. Individuals were identified with the electronic databases of the regional municipal administration registration. The overall design of the COCOS (COlonoscopy or COlonography for Screening) trial has been described in detail previously.(16) Ethics approval was obtained from the Dutch Health Council (2009/03WBO, The Hague, Netherlands). All participants gave their written informed consent.

Randomization and masking

Individuals were randomly assigned (2:1) to colonoscopy or CT colonography for primary screening for CRC. The trial originated from two different projects: one for colonoscopy screening and one for CT colonography screening, was separately funded, but could be merged into this randomized trial, which explains the 2:1 ratio. Randomization was done before invitation, to mimic a true population-based screening program. Randomization was done per household, to prevent individuals from switching invitations or calling the screening centre to be assigned to another group of the study. Additionally, individuals were stratified for age (50–54, 55–59, 60–64, 65–69, 70–75 years), sex, and socioeconomic status (score 1–5; very low, low, average, high, very high). These details were based on the Dutch population registry and on data from Statistics Netherlands, providing information on which socioeconomic status is linked to each postal code in the Netherlands. This way the invited population was representative for the Dutch population of 50 to 75 years in terms of sex, socioeconomic status, incidence and mortality of CRC, and access to medical care.

Randomization was done by TENALEA using ALEA Randomization software (version 2.2), with TENALEA online resource for clinical trials, providing various validated algorithms for randomization of individuals in clinical trials. For this study, we used the TENALEA minimisation algorithm based on Pocock and Simon. (17)

Minimisation conceals treatment allocation since it does not use a predefined allocation scheme, but assigns treatment on the basis of characteristics of the individuals and the treatment assignment of participants already randomized in the study. Invitees and screening centre employees were not masked from the allocation.

Procedures

All individuals were invited by mail between June 8, 2009, and August 16, 2010, by the regional comprehensive cancer centres. Invitations were accompanied by an information leaflet, including information about CRC in general, and about advantages and possible risks of colonoscopy or CT colonography (only about the test for which the person was invited), derived from previous pilots of CRC screening and approved by the Dutch Health Council.(18-20) Further details about the information leaflets and invitation letters are provided in the **Web appendix 1.**

Invitees with symptoms potentially related to CRC in the previous 3 months (e.g., rectal blood loss or changed bowel habits, or both) were recommended to decline the invitation for screening and contact their family doctor instead. All invitees invited in this study will be linked to the national cancer registry for follow-up on incidence (including left-sided and right-sided cancers) and mortality attributable to CRC over a 10-year period since invitation.

Invitees in both groups were offered screening with a previous consultation with a doctor or nurse. During the consultation, the procedure, risks, general health status, and informed consent were discussed. Respondents were excluded from participation if they had had a colonoscopy, CT colonography, or double-contrast barium enema in the previous 5 years, or if they had severe disease with a life expectancy of less than 5 years. This strategy was in line with international Recommendations for CRC screening. (21) CT colonography responders were also excluded in case of pregnancy, hyperthyroidism, iodine contrast medium allergy, or when they had been exposed to ionising radiation for research purposes within the previous 12 months.

All colonoscopies were scheduled on one of the programs of five experienced gastroenterologists (≥1000 colonoscopies) and done according to the standard quality indicators defined by the Society of Gastrointestinal Endoscopy. (22) For bowel preparation, we used 2 L of polyethylene electrolyte glycol solution (Moviprep, Norgine bv, Amsterdam, Netherlands) together with 2 L of transparent fluid, and a low-fibre diet for 2 days. Conscious sedation (midazolam) and analgesics (fentanyl) were given intravenously at the discretion of the participant and the endoscopist. Hyoscine butylbromide was given intravenously at the start of withdrawal of the endoscope to reduce colonic motility if needed. Withdrawal time was at least 6 minutes. Of all detected lesions, morphology (sessile, pedunculated, flat, or depressed), location (distance from the anus and segment), macroscopic aspect (hyperplastic, adenomatous, carcinomatous) and size (open biopsy forceps with 7 mm span) were noted. If possible, all detected lesions were removed during the same procedure and, if not, biopsies were obtained for histopathology. We used final histopathology outcome of these lesions as the definitive diagnosis.

For participants assigned to receive CT colonography, a non-cathartic preparation consisting of two times 50 ml of iodinated contrast agent (Telebrix Gastro, Guerbet, Aulnaysous-Bois, France) was given on the day before the examination, 50 ml 1.5 h before the examination, and a low-fibre diet for 1 day. Colonic distension was obtained with an automatic carbon dioxide insufflator (PROTOCO2L, Bracco, EZEM, Lake Success, NY, USA) after intravenous administration of 20 mg hyoscine butylbromide. If contraindicated, 1 mg of glucagon hydrochloride was used intravenously. If both bowel relaxants were contraindicated, no medication was used. We obtained CT images in the supine and prone position on two 64-slice CT-scanners (Brilliance, Philips Healthcare, Best, Netherlands; SOMATOM Sensation, Siemens Medical Solutions, Erlangen, Germany) using a low-dose protocol; with collimation 64 × 0.625 mm, slice thickness 0.9 mm, reconstruction interval 0.7 mm, tube voltage 120 kV, and 25 reference mAs (for Brilliance) and collimation 128 × 0.6 mm, slice thickness 1.0 mm, reconstruction interval 0.7 mm, tube voltage 120 kV, and 16 ref mAs (for SOMATOM Sensation). Lesion detection was done by one of three experienced readers (≥800 examinations). Images were read in primary 2D (window setting 1500, –250 HU) with 3D problem solving using enhanced 3D visualisation software (View Forum, Philips, Best, Netherlands), followed by secondary computer-aided detection (CAD) read using a commercial CAD system of Philips healthcare (non-commercial outside Europe). CT colonography was done with non-cathartic bowel preparation and low-dose protocol, and therefore a primary three-dimensional read (either with or without electronic cleansing) was not appropriate. For experienced readers, a primary two-dimensional read has been shown to be as accurate as a primary three-dimensional read and two-dimensional read turned out to be more time efficient. (23) We examined extracolonic structures using the C-RADS classification.(24) We judged an extracolonic lesion C-RADS E3 or E4 to be possibly clinically relevant.

Follow-up after a positive test result

Colonoscopy participants were informed about the findings on the day of the procedure, and, in case of histology sampling, were informed within 2 weeks by telephone on the definitive diagnosis. Recommendations about surveillance colonoscopy were given according to Dutch adenoma surveillance guidelines.(25) In case of cancer, staging investigations were done and the patient was referred for further treatment. CT Colonography participants were informed by telephone about the CT colonography results within 2 weeks. Participants with one or more large lesions (≥10 mm) who had had a CT colonography were referred for colonoscopy within 3 weeks, during which CT colonography findings were revealed with segmental unblinding, which was done by a physician or nurse from the radiology department. All polyps detected during follow-up colonoscopy were removed, irrespective of size.

By contrast with US screening guidelines for CRC (26), the Dutch Health Council decided that participants with less than three lesions measuring 6–9 mm should be recommended to undergo surveillance CT colonography after 3 years, whereas participants with three or more lesions measuring 6–9 mm were recommended follow-up CT colonography after 1.5 years. Polyps smaller than 6 mm were ignored because of the very low prevalence of malignancy in these lesions.(27) Participants with relevant extracolonic findings were referred for corresponding tests.

Histology was assessed by two expert gastrointestinal pathologists and defined according to the Vienna criteria.(28) Lesions were classified as hyperplastic polyp, serrated adenoma, adenoma (tubular, tubulovillous, or villous), or carcinoma. Dysplasia was defined as low-grade or high-grade. Advanced adenoma was defined as an adenoma of 10 mm or more, or as an adenoma (irrespective of size) with at least 25% villous histology or with high-grade dysplasia, or both.(29) Advanced neoplasia was defined as either advanced adenoma or CRC.

Complications related to colonoscopy and CT colonography were recorded at the time of the procedure. All participants were contacted 2 weeks after the procedure for registration of post-procedural complications and were instructed to contact the primary investigator if complications occurred in the additional 2 weeks.

Statistical analysis

The analysis was based on the intention-to-treat principle. The primary endpoint, participation rate, was defined as the number of participants undergoing the screening test relative to the total number of invitees. Results were not adjusted for clustering, because in most instances there were only one or two eligible individuals per household. Diagnostic yield was calculated as number of participants with advanced neoplasia relative to the total number of participants and relative to the total number of invitees. Differences were expressed as relative risk with 95% CIs. We used logistic regression to test the statistical significance of the difference in participation and detection rates between groups, taking into account the factors used in the randomization. Two-sided p values of less than 0.05 were deemed significant. We used SPSS for Windows, version 18, for all the analyses.

We predicted a participation rate of 25% in colonoscopy screening and 35% in CT colonography screening, on the basis of the participation rate of sigmoidoscopy screening in the Netherlands. (18) By inviting at least 7,500 individuals, a statistical power of more than 99% would be achieved to reject the null hypothesis of no difference, using a $\chi 2$ test with a significance level set at 0.05. We aimed for high precision on the primary outcome to provide an optimum basis for political and public health decision making on introduction of a population-based program of CRC screening in the Netherlands. The invitation process continued until at least 1,250 colonoscopies

and 875 CT-colonographies were done. This trial was registered in the Dutch trial register, number NTR1829.

Role of the funding source

The sponsors of the study had no access to the data, no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between June 8, 2009, and August 16, 2010, 8,844 people were randomly allocated to be invited to screening with colonoscopy or CT colonography (**Figure 1**). Colonoscopy invitees had a mean age of 60.8 years (SD 6.6), a mean socioeconomic status of 3.0 (SD 1.4), and 50% of them were male. CT colonography invitees had a mean age of 60.9 years (SD 6.7), a mean socioeconomic status of 3.0 (SD 1.4), and 49% of them were male. Overall, 1,276 (22%) of 5,924 colonoscopy invitees participated compared with 982 (34%) of 2,920 CT colonography invitees (relative risk [RR] 1.56 [95% CI 1.46–1.68]

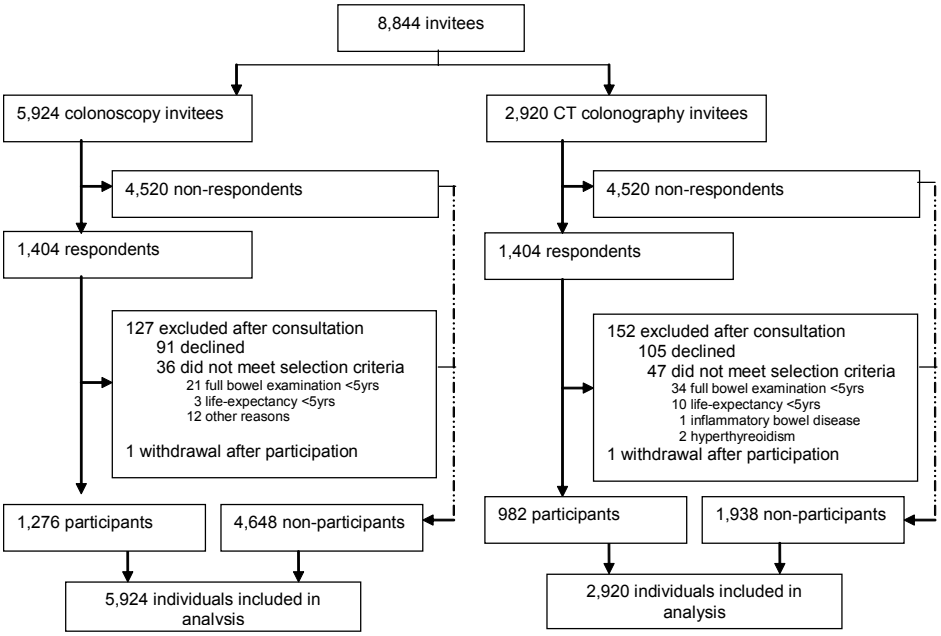

Figure 1: Participation and outcome among colonoscopy and CT colonography invitees.

Table 1: Participation rate by age, sex and socioeconomic status

	Colonoscopy		CT Colonography	
	Invitees[a] n=5,924	Participants[a] n=1,276	Invitees[a] n=2,920	Participants[a] n=982
Age (years)				
50-54	1,277	290 (23%)	621	230 (37%)
55-59	1,423	334 (23%)	742	264 (36%)
60-64	1,439	306 (21%)	665	219 (33%)
65-69	1,009	245 (24%)	497	171 (34%)
70-75	772	101 (13%)	395	98 (25%)
p value	..	<0.0001[b]	..	0.001[b]
Sex				
Male	2,937	652 (22%)	1,439	507 (35%)
Female	2,987	624 (21%)	1,481	475 (32%)
p value		0.22[b]		0.07[b]
Socioeconomic Status				
Very low	1,030	178 (17%)	546	169 (31%)
Low	1,236	257 (21%)	568	187 (33%)
Average	1,160	261 (23%)	588	184 (31%)
High	1,127	257 (23%)	606	231 (38%)
Very high	1,206	306 (25%)	528	191 (36%)
p value		0.0001[b]		0.04[b]

The denominator of all percentages is the number of invitees in the corresponding category.
[a] Due to missing values, the total number of participants included in the analyses per age and socioeconomic status do not always add up to the total number of invitees or participants.
[b] p values were for the comparison of participation rates between subgroups and were calculated with $\chi 2$ statistics.

p<0.0001). **Table 1** shows details on participation rate by age, sex, and socioeconomic status.

The most frequently mentioned reasons for non-participation are summarised in **Web appendix 2.** Participation rates in colonoscopy and CT colonography screening differed significantly between age groups and between socioeconomic categories, with lower participation in advanced age groups and lower socio economic categories. Participation did not differ between men and women. 43 (3%) of 1276 colonoscopy participants had at least one first-degree relative aged 49 years or younger with CRC or at least two first-degree relatives aged 50 years or older with CRC, compared with 34 (3%) of 982 CT colonography participants.

Colonoscopy was incomplete in 39 (3%) of 1,276 colonoscopy participants because of poor bowel preparation (n=21), pain during the procedure (n=8), bowel anatomy (n=6), presence of a colonic stricture (n=2), or other (n=2). The procedure was suc-

cessfully repeated in 11 participants, 28 declined re-examination, resulting in an overall completion rate of 98%. CT colonography was incomplete in 44 (4%) of 982 participants because of inadequate distension (n=29), inadequate tagging (n=12), or both (n=3). It was successfully repeated in 33 participants, 11 declined re-examination, resulting in an overall completion rate of 99%.

Of all 982 CT colonography participants, 78 (8%) were offered surveillance after 3 years and four (<1%) after 18 months because of 6–9 mm lesions. These surveillance data are not yet available for analysis. Another 84 (9%) were referred for colonoscopy because they had at least one large lesion (≥10 mm). All these individuals underwent colonoscopy. Two of these 84 colonoscopies were initially incomplete because of a post-polypectomy bleeding and insufficient bowel preparation, but successfully repeated. In seven (8%) participants, no lesions were found on colonoscopy.

In the primary colonoscopy group, 111 participants were diagnosed with advanced neoplasia, compared with 60 CT colonography participants **(Table 2),** corresponding with at least one advanced neoplasia in 8.7 per 100 colonoscopy participants vs. 6.1 per 100 CT colonography participants (RR 1.46; 95% CI 1.06–2.03; p=0.02). Relative to those invited, the difference is 1.9 per 100 vs. 2.1 per 100 invitees (RR 0.91, 0.66–2.03, p=0.56). The positive predictive value for advanced neoplasia of CT colonography was 71% (95% CI 0.62–0.81). If CAD had not been used in CT colonography, this would have resulted in 59 instead of 60 participants with advanced neoplasia.

In the primary colonoscopy group, 87 participants were diagnosed with advanced neoplasia of 10 mm or more, compared with 58 CT colonography participants (Table

Table 2: Most advanced lesion per participant and per invitee for colonoscopy and CT colonography (CTC)

	Yield per 100 participants			Yield per 100 invitees		
	Colonoscopy (n=1,276)	CTC (n=982)	p value	Colonoscopy (n=5,924)	CTC (n=2,920)	p value
Colorectal cancer (n)[a]	0.5 (7)	0.5 (5)	0.91	0.1 (7)	0.2 (5)	0.50
Advanced adenoma (n)	8.2 (104)	5.6 (55)	0.02	1.8 (104)	1.9 (55)	0.69
≥10 mm	6.3 (80)	5.4 (53)	0.30[b]	1.4 (80)	1.8 (53)	0.11[b]
Non-advanced adenoma (n)	21.4 (273)	1.2 (12)	<0.0001	4.6 (273)	0.4 (12)	<0.0001
Serrated adenoma (n)	2.4 (32)	0.2 (2)	<0.0001	0.5 (32)	0.1 (2)	0.001
Hyperplastic polyp (n)	13.9 (178)	0.3 (3)	<0.0001	3.0 (178)	0.1 (3)	<0.0001
Advanced neoplasia (n)	8.7 (111)	6.1 (60)	0.02[c]	1.9 (111)	2.1 (60)	0.56
≥10 mm	6.8 (87)	5.9 (58)	0.31[d]	1.5 (87)	2.0 (58)	0.07

Numbers in brackets are the actual number of individuals.

[a] All CRCs were 10 mm or larger.

[b] Relative risk for advanced adenomas of 10 mm or more per 100 participants was 1.17 (95% CI 0.82-1.68), relative risk for advanced adenomas of 10 mm or more per 100 invitees was 0.74 (0.52-1.05)

2; for participants, RR was 1.17, 95% CI 0.83–1.64, p=0.31; for invitees, RR was 0.74, 0.53–1.03, p=0.07).

Tables 3 and 4 summarize the characteristics of detected advanced adenomas and cancers. In the 111 colonoscopy participants with advanced neoplasia, 140 advanced adenomas were detected. Of these, 104 (74%) were at least 10 mm, 72 (51%) showed a 25% or more villous component, and 36 (26%) contained high-grade dysplasia (Table 3). Both advanced and non-advanced lesions were mostly sessile and most advanced lesions were left sided (Table 4). In the 60 CT colonography participants with confirmed

Table 3: Histology and dysplasia of detected adenomas

	Colonoscopy (n, %)	CT Colonography (n,%)
Adenomas ≥10 mm		
Villous	2 (2%)	1 (2%)
HGD	1 (1%)	0
Tubulovillous	50 (48%)	38 (58%)
HGD	6 (6%)	6 (9%)
Tubular	49 (47%)	26 (39%)
HGD	5 (5%)	3 (5%)
Not specified	3 (3%)	1 (2%)
Total	104	66
Adenomas 6-9 mm		
Villous	0	0
High grade dysplasia	0	0
Tubulovillous	12 (11%)	3 (8%)
High grade dysplasia	2 (2%)	0
Tubular	98 (87%)	33 (85%)
High grade dysplasia	4 (4%)	0
Not specified	3 (3%)	3 (8%)
Total	113	39
Adenomas 6-9 mm		
Villous	0	0
High grade dysplasia	0	0
Tubulovillous	8 (2%)	5 (5%)
High grade dysplasia	6 (1%)	0
Tubular	98 (87%)	33 (85%)
High grade dysplasia	12 (2%)	2 (2%)
Not specified	12 (2%)	17 (17%)
Total	495	98
Total number of adenomas	**712**	**203**
Total number of advanced adenomas	**140**	**76**

Table 4: Morphology of detected adenomas and location of colorectal cancers and advanced adenomas

	Colonoscopy (n, %)	CT Colonography (n,%)
Morphology		
Advanced adenomas	140	76
Flat	6 (4%)	5 (7%)
Sessile	71 (51%)	26 (34%)
Pedunculated	62 (44%)	43 (57%)
Missing	1 (1%)	2 (3%)
Non-advanced adenomas	572	127
Flat	31 (5%)	17 (13%)
Sessile	477 (83%)	97 (76%)
Pedunculated	44 (8%)	8 (6%)
Missing	20 (3%)	5 (4%)
Location		
Colorectal cancers	7	5
Rectosigmoid	5 (71%)	4 (80%)
Proximal[a]	2 (29%)	1 (20%)
Advanced adenomas	140	76
Rectosigmoid	85 (61%)	50 (66%)
Proximal[a]	55 (39%)	26 (34%)

[a] Proximal is defined as descending colon, transverse colon, ascending colon or caecum (as Atkin and colleagues[30]).

advanced neoplasia, 76 advanced adenomas were detected. Of these, 66 (87%) were at least 10 mm, 47 (62%) showed a 25% or more villous component, and 11 (14%) contained high-grade dysplasia (Table 3). Most advanced lesions were pedunculated and left sided (Table 4). Most non-advanced lesions were sessile (Table 4).

Seven (<1%) of the 1,276 colonoscopy participants had a carcinoma, compared with five (<1%) of the 982 CT colonography participants; p=0.90. All CRCs were 10 mm or larger. Eleven (92%) of these carcinomas were classified as Dukes A and one carcinoma, detected in a colonoscopy participant, was classified as Dukes C.

Serious adverse events included post-polypectomy bleeding in two colonoscopy participants (0.2%) and in three CT colonography participants (0.3%) who received subsequent colonoscopy. One colonoscopy participant died 22 days after colonoscopy because of a spinal epidural abscess, not likely related to the colonoscopy. Complications are further described in **Table 5.**

Potentially important findings (C-RADS E3 or E4) were detected in 107 CT colonography participants (11%), of whom 94 (10%) had a new diagnosis for which they

Table 5: Complications within 30 days after the examination among colonoscopy and CT colonography participants

	Colonoscopy (n, %)	CT Colonography (n,%)
Serious adverse events[b]		
Post-polypectomy bleeding	2	3
Atrial fibrillation	1	0
Collapse	1	1
Pneumonia	1	0
Spinal epidural abscess[c]	1	0
Acute coronary syndrome	0	1
Acute rheumatic fever	0	1
Cerebrovascular accident	0	1
Myocardial infarction	0	1
Other adverse events[d]		
Urinary-tract infection	1	0
Ingestion of disinfectant (30% alcohol) instead of 50 ml iodinated contrast agent	0	1

[a] All complications occurred after CT colonography, except for the post-polypectomy bleedings and the ingestion of disinfectant instead of 50 ml of iodinated contrast agent.
[b] Serious adverse events were defined as events leading to hospital admission or extension of hospital stay.
[c] Participant died 22 days after colonoscopy. This complication seemed not to be related to the colonoscopy, but to concurrent otitis media.
[d] Other adverse events were defined as events other than serious adverse events.

were further assessed. No complications occurred during further assessments, which showed extracolonic cancer in five participants (four renal-cell carcinomas and one duodenal carcinoma), abdominal aortic aneurysms in seven participants (three underwent surgical treatment), and aneurysms of smaller vessels in three participants. One participant had low-risk myelofibrosis, one had Paget's disease, and another had a suspected lung lesion which, after lobectomy, turned out to be a glandular papilloma. The remaining C-RADS E3 and E4 findings turned out to be benign lesions, 19 located in the kidney, 12 in the gynaecological organs, seven in the liver, seven in the lung, five in the adrenals, and 26 in other organs.

DISCUSSION

We compared participation and diagnostic yield of colonoscopy and non-cathartic CT colonography for primary CRC screening in a population-based randomized trial with individuals aged 50–75 years. The participation rate was higher with CT colonography than with colonoscopy, whereas colonoscopy identified more advanced neoplasia in

participants than did CT colonography. These two differences more or less cancelled each other out in the diagnostic yield per invitee, which was similar in both groups (**Panel**).

Panel. Research in context

Systematic review

We searched PubMed for studies comparing participation and diagnostic yield of colonoscopy and CT colonography screening. Several studies compared the accuracy and yield of colonoscopy and CT colonography in an average-risk population.(15;31-33) However, the effectiveness of a screening program does not only depend on detection rate, but also on participation. Only one previous study addressed the participation rate and yield of screening in an average-risk population with either colonoscopy or CT colonography.(34)

Interpretation

Our results show that colonoscopy and CT colonography screening result in a lower participation rate compared to guaiac-based faecal occult blood test (gFOBT) and FIT screening.(18-20) The participation rate of sigmoidoscopy screening was similar to that of CT colonography.(18) The yield of advanced neoplasia per 100 invitees was similar between colonoscopy and CT colonography, and to that noted with flexible sigmoidoscopy (18), and higher than that noted with first-round gFOBT or faecal immunochemical test.(18-20) Both gFOBT and sigmoidoscopy screening have been proven to decrease colorectal cancer-related mortality.(4;30) Whether screening with colonoscopy or CT colonography lowers the mortality related to colorectal cancer is unknown in absence of large, long-term prospective controlled trials. In deciding which screening technique would be preferable, we should keep in mind that the detection rates for advanced neoplasia might be different in subsequent screening rounds and that participation rates might change over these rounds. Additionally, other factors such as cost-effectiveness and experienced burden should be taken into account.

Because the screening naive invitees were directly selected from the population registry, without any pre-selection strategy, our results are representative for the general Dutch population. Invitations for colonoscopy and CT colonography were sent by postal mail in the same period, to minimise the possibility of participation being affected by external influences such as public awareness. Yet, during the screening trial, there was no nationwide screening program or awareness campaign for CRC in the Netherlands, which might have influenced our participation rate in a negative way.

Unfortunately, no follow-up data are available yet on the participants offered CT colonography surveillance. On the basis of the diagnostic yield in our colonoscopy group, we can expect that the diagnostic yield of CT colonography has been underestimated with respect to 6–9 mm advanced neoplasia. We detected advanced neoplasia of 10 mm or more in 1.5 per 100 colonoscopy invitees and in 2.0 per 100 CT colonography invitees, respectively. If the cut-off value for referral would have been 6 mm or more rather than at least 10 mm, we would probably have noted a higher diagnostic yield. Given the small number of CRCs detected and the size of our study group, we were unable to obtain a precise comparison of the diagnostic yield for CRCs. The diagnostic yield of CT colonography screening might not unconditionally

be generalised to other settings, in which the experience of CT colonography readers might be lower than in our study. However, results from a study showed that inexperienced readers can reach a similar sensitivity compared with experienced readers after 175 CT colonographies with colonoscopy verification. (35)

It can be debated whether the use of non-cathartic preparation in our study has influenced the diagnostic yield in the CT colonography group in a positive or negative way. To our knowledge, no studies have compared the diagnostic accuracy of CT colonography with cathartic or non-cathartic preparation. However, several studies with iodine tagging similar to that in our study showed results close to those with cathartic preparation.(13;14) Results from a previous study in which 48% of participants were symptomatic, showed that the use of non-cathartic preparation consisting of 200 ml iodinated contrast agent, resulted in a per patient sensitivity of 90–94% for polyps of 6 mm or more.(14) Another study done in a population positive for faecal occult blood test (FOBT), reported results on differences in diagnostic accuracy, between a bowel preparation consisting of 350 ml (group 1) vs. 200 ml (group 2) iodinated contrast agent.(13) The mean sensitivity per patient for large lesions (≥10 mm) did not differ significantly between both preparation schemes (90% group 1 *vs.* 96% group 2, respectively). For lesions of 6 mm or more, one of the two observers reached a significant difference in per patient sensitivity, as preparation 1 resulted in a sensitivity of 82%, whereas preparation 2 resulted in a sensitivity of 98%. No differences in per patient specificity were recorded. Therefore, we think that the use of non-cathartic preparation did not influence the diagnostic yield of CT colonography screening in a negative way.

To our knowledge, only one other randomized trial comparing participation and diagnostic yield of colonoscopy and CT colonography has been published so far.(34) That study, a community-based screening trial in Australia, reported participation rates of 16% for colonoscopy and 18% for CT colonography, and a diagnostic yield for advanced neoplasia of 8.4 per 100 and 9.0 per 100 participants, respectively.(34) The main differences with our study were the substantially smaller numbers of invitees (n=1,400 *vs.* 8,844) and the fact that invitees who met the exclusion criteria were excluded before the analyses, thereby artificially increasing the participation rate. Diagnostic yield in the colonoscopy group was similar to the one in our study, whereas the diagnostic yield of CT colonography was higher, which could be explained by the use of other referral criteria. (35)

The 22% participation rate in our colonoscopy group is more than double the 10% participation rate for colonoscopy reported in an Italian randomized trial of screening for CRC. (36) In another similar trial of average risk individuals selected by general physicians in Italy, the participation rate for colonoscopy was 27%.(37) Differences with our study are the procedure for selection of invitees and exclusion before ran-

domization. The participation rate in our CT colonography group was 34%. To our knowledge, apart from the Australian randomized trial reporting a participation rate of 18%, no other studies have previously reported on participation rates for CT colonography with primary population screening. (34)

Our findings on detection rates are similar to other studies. In our study, advanced neoplasia was detected in 8.7% of colonoscopy participants, which was similar to German reports in which advanced neoplasia was reported in 7.9% of average risk individuals aged 55–99 years.(38) Another study done in the USA including asymptomatic individuals from 13 Veterans Affairs medical centres aged 50 years or older (97% men), reported advanced neoplasia in 10.5% of colonoscopy participants.(39) The higher incidence of advanced neoplasia in their study might be explained by the higher prevalence of a positive family history: 13.9% compared with 3.4% in our study, and the strong male predominance. A third study including individuals older than 20 years, which was also done in the USA, showed a somewhat low detection rate for advanced neoplasia of 5.9%.(40) The same detection rate of 5.9% was reported in a Polish study in participants aged 50–66 years, despite 13.3% of participants reporting a positive family history.(41) A fifth study done in the USA including predominantly asymptomatic individuals (98%) and with 8.4% of participants having a positive family history, detected advanced neoplasia in 3.4% of participants.(15)

By referring almost 9% of CT colonography participants for colonoscopy because of large lesions (≥10 mm), we detected advanced neoplasia in 6.1% of the participants (detection rate in referred individuals 75%). This diagnostic yield seems high. One similar study had a similar referral rate of 7.9% and advanced neoplasia was detected in 3.2% of participants (detection rate 41%).(15) However, these results also include an unknown number of referred participants with only 6–9 mm lesions detected at CT, who were given the choice between immediate colonoscopy and surveillance CT colonography. It is unclear how many participants were detected with CT lesions of 10 mm or more in previous studies comparing the diagnostic value of CT colonography and colonoscopy in average risk individuals, as the detected advanced neoplasia was not presented by referring CT-size categories.(12)

We detected a low number of fl at adenomas by both colonoscopy and CT colonography (Table 4). These results are similar to those of a previous study reporting on the prevalence of flat neoplasms.(42) In that study, 9% of detected neoplasms in screening participants were flat.(42)

When comparing colonoscopy and CT colonography, some important aspects need to be considered. Colonoscopy has the advantage that detected lesions can be removed immediately, whereas CT colonography participants need a subsequent colonoscopy. CT colonography has the advantage that the risk of complications is low (15), whereas colonoscopy has a 0.1–0.3% risk of complications.(10;11) In our study, three post-

polypectomy bleedings occurred in the CT colonography group (0.3% of participants) and two post-polypectomy bleedings occurred in the colonoscopy group (0.2%). The finding of similar complication rates is not unexpected as CT colonography screening will also result in colonoscopy-related complications in those participants referred for polypectomy of large lesions with increased risks of complications.(10) Additionally, in both groups, a few serious adverse events occurred, which seemed not directly related to the procedure, but related to the age and comorbidity of the screenees. A disadvantage of CT colonography is the exposure to ionising radiation, whereas the visualisation of extracolonic structures is both an advantage and a disadvantage. A study assuming a substantially higher dose than that used in this study, estimated that the number of CRCs prevented with a 5-year screening interval outweighs the number of radiation-related cancers (benefit-risk ratio 24:1) (43)

In our study, colonoscopy detected 273 non-advanced adenomas in 1,276 individuals, whereas CT colonography showed 12 non-advanced adenomas in 982 participants (no surveillance data are available yet). Smaller adenomatous lesions have a low prevalent risk of bearing dysplasia or cancer, although we are not able to predict which lesions will progress over time. Besides, more hyperplastic lesions were detected by colonoscopy compared with CT colonography. One can defend the argument that it is an attractive feature of CT colonography that it finds fewer smaller adenomas and hyperplastic lesions, since every polypectomy is associated with risks, as well as increased burden, and costs. Altogether, one can argue both ways with respect to the lower sensitivity of CT colonography; for the short term it prevents further intervention, for the long term, it is likely to limit the preventive effect of the screening intervention.

Since the invitational processes for colonoscopy and CT colonography in our study were identical, the most probable reason for the significant difference in participation rate is a difference in the expected burden or procedure-related complications. In the Netherlands, several trials of screening for CRC have been done in the past few years. (18-20) The Dutch participation rates of screening for guaiac-based FOBT (47–50%) and faecal immunochemical test (FIT; 60–62%) were higher than the participation rates of colonoscopy and CT colonography noted in this study.(18;19) Sigmoidoscopy screening had a participation rate of 32% in the Netherlands, which was similar to CT colonography screening.(18) Participation rates of all screening techniques could be increased by increasing public awareness through large campaigns, or by involving more actively general practitioners in the invitation process. Although both guaiac-based FOBT and FIT had a higher participation rate than did other available screening techniques, the diagnostic yield of 0.6 and 1.4–1.5 per 100 invitees, respectively, were lower than those with sigmoidoscopy, colonoscopy, and CT colonography screening (2.2, 1.9, and 2.1 per 100 invitees, respectively). Whether screening for CRC with FIT, colonoscopy, and CT colonography lowers colorectal cancer-related mortality

is unknown in the absence of large, long-term prospective controlled trials. Both guaiac-based FOBT and sigmoidoscopy screening have in such studies been proven to decrease mortality related to CRC by 16% and 31%, respectively (4;30)

In deciding which screening technique is favourable, we should keep in mind that the detection rates for advanced neoplasia might be different in subsequent screening rounds and that participation rates might change over these rounds. The decision about the preferred method for CRC screening in population-based screening can be guided by the results of our trial, which showed more participants with non-cathartic CT colonography, a higher yield for colonoscopy, but a similar diagnostic yield for both methods in the detection of advanced neoplasia per 100 invitees. Therefore, to know which screening technique is preferable, other factors such as cost-effectiveness, influenced by higher participation rate of CT colonography and higher yield per participant for colonoscopy, and experienced burden should be studied. Details about experienced burden (as obtained in our trial) and about cost-effectiveness will be reported elsewhere.

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APPENDICES

Webappendix 1

Available online (Lancet Oncology), includes:

- Information on 'development of information leaflets and invitation letters'
- Information leaflets as used during the COCOS trial
  - o colonoscopy, intake at the outpatient clinic
  - o colonoscopy, intake by telephone
  - o CT colonography, intake by telephone
- Invitation letters as used during the COCOS trial
  - o colonoscopy, intake at the outpatient clinic
  - o colonoscopy, intake by telephone
  - o CT colonography, intake by telephone

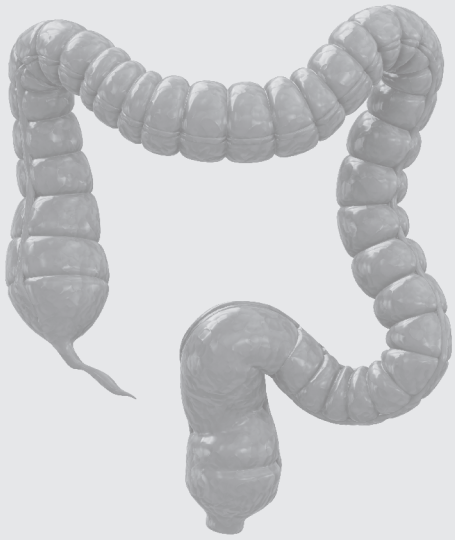
Webappendix 2: Most frequently mentioned reasons for non-participationa

Reason	Colonoscopy	CT colonography
I have symptoms suggestive for CRC	35 (1%)	10 (1%)
I have recently undergone a colonoscopy	398 (9%)	185 (10%)
I have recently undergone a barium contrast enema	44 (1%)	23 (1%)
I am coping with another illness	141 (3%)	48 (2%)
Other reason	784 (17%)	279 (14%)
I do not want to indicate a reason for non-participation	1,249 (27%)	510 (26%)
No response	1,941 (42%)	864 (45%)
Died/moved	56 (1%)	19 (1%)
Total number of non-participants	4,648 (100%)	1,938 (100%)

[a] Reasons for non-participation as indicated on the reply card (including excluded subjects).

CHAPTER 3

Burden of Colonoscopy Compared to Non Cathartic CT Colonography in a Colorectal Cancer Screening Program: Randomized Controlled Trial



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ABSTRACT

Objective: CT colonography has been suggested to be less burdensome for primary CRC screening than colonoscopy. We compared the expected and perceived burden of both in a randomized trial.

Design: 8,844 Dutch citizens aged 50-74 were randomly invited for CRC screening with colonoscopy (n=5,924) or CT colonography (n=2,920). Colonoscopy was performed after full colon lavage, CT colonography after limited bowel preparation (non-cathartic). All invitees were asked to complete the expected burden questionnaire (EBQ) before the procedure. All participants were invited to complete the perceived burden questionnaire (PBQ) 14 days afterwards. Mean scores were calculated on five-point scales.

Results: *Expected burden:* 2,111 (36%) colonoscopy and 1,199 (41%) CT colonography invitees completed the EBQ. Colonoscopy invitees expected the bowel preparation and screening procedure to be more burdensome than CT colonography invitees: mean scores 3.0±1.1 versus 2.3±0.9 ($p<0.001$) and 3.1±1.1 versus 2.2±0.9 ($p<0.001$).

Perceived burden: 1,009/1,276 (79%) colonoscopy and 801/982 (82%) CT colonography participants completed the PBQ. The full screening procedure was reported as more burdensome in CT colonography than in colonoscopy: 1.8±0.9 versus 2.0±0.9 ($p<0.001$). Drinking the bowel preparation received a higher burden score in colonoscopy (3.0±1.3 versus 1.7±1.0, $p<0.001$) while related bowel movements were scored more burdensome in CT colonography (2.0±1.0 versus 2.2±1.1, $p<0.001$). Most participants would probably or definitely take part in a next screening round: 96% for colonoscopy and 93% for CT colonography ($p=0.99$).

Conclusion: In a CRC screening program, colonoscopy invitees expected the screening procedure and bowel preparation to be more burdensome than CT colonography invitees. In participants, CT colonography was scored as more burdensome than colonoscopy. Intended participation in a next screening round was comparable.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

- Population screening for colorectal cancer (CRC) should lead to a reduction in CRC-related mortality.
- Colonoscopy and CT- colonography are both accurate methods for the detection of colorectal neoplasia and can be used for population-based CRC screening.
- CT colonography has been shown to be superior in terms of overall patients' preference in tandem-studies.

WHAT ARE THE NEW FINDINGS?

- Colonoscopy invitees expected the screening procedure to be more burdensome than CT colonography invitees.
- CT colonography participants perceived the screening procedure as more burdensome than colonoscopy participants.
- Intended participation in a future screening round was comparable.

HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FORESEEABLE FUTURE?

- Results may attenuate some of the advantages of CT colonography compared to colonoscopy in a screening setting.
- Although CT colonography participants perceived the screening procedure as more burdensome, it remains to be seen whether this will result in a difference in actual participation to future screening rounds, as intended participation was comparable.

BACKGROUND

Each year, more than 400,000 persons are diagnosed with colorectal cancer (CRC) and half of them die from the disease.(1) CRC incidence can be decreased by timely detection of CRC and removal of colonic adenomatous polyps.(2) Early detection of adenomas and CRC is possible through population screening programs, which should lead to a reduction in CRC-related mortality and maybe also incidence.(3;4)

The population health gain of a screening program is affected not only by the accuracy of the screening test, but also by the corresponding participation rate. Initial participation can be influenced by the expected burden of the screening test. Those who anticipate the screening procedure to be burdensome may be less likely to take part. The actually perceived burden of the procedure, from beginning to end, could play a role in future program adherence.

Colonoscopy and CT colonography are both accurate methods to visualize the entire colon. Colonoscopy is considered as the reference standard for detection of colonic neoplasia while CT colonography has a high estimated per-patient sensitivity (88%) for large adenomas.(5) CT colonography has been shown to be superior in terms of overall patient preferences.(6-9) Previous CT colonography studies were non-randomized and used a tandem design, in which CT colonography was per-

formed prior to colonoscopy. This gives participants the opportunity to compare the perceived burden of both techniques but suffers from having a fixed sequential order. To our knowledge no studies have been published comparing both the expected and perceived burden of colonoscopy and CT colonography.

Within a randomized controlled trial we compared the expected burden of a population-based colorectal cancer screening using either primary colonoscopy or CT colonography, as well as the perceived burden and participants' willingness to return in future screening rounds. One would expect that colonoscopy invitees would anticipate the procedure to be more burdensome than CT colonography invitees. In addition, CT colonography participants can be expected to perceive the screening as less burdensome, especially because of the limited bowel preparation used in CT colonography, compared to the extensive bowel preparation needed for colonoscopy.(8) A lower patient burden may be reflected in a larger proportion of CT colonography participants expressing a willingness to return in future screening rounds.

METHODS

Patients and settings

Between June 2009 and July 2010, a total of 8,844 Dutch citizens aged 50-74 years were invited by mail for population-based CRC screening in the regions of Amsterdam and Rotterdam. The trial protocol has been described in detail elsewhere.(10) Invitations were randomly allocated 2:1 to colonoscopy (n=5,924) or CT colonography (n=2,920) by a computerized randomization program (ALEA Randomization Service).(11) Invitees within a single household were invited to the same modality. Allocation was stratified for age, sex and socio-economic status based on data of Statistics Netherlands.(12) Invitees could not opt for the alternative screening strategy. At the time of the trial, the Netherlands did not have population-based CRC screening programs. Ethics approval was obtained from the Dutch Health Council (2009/03WBO, The Hague, The Netherlands). The trial was registered in the Dutch Trial Register: NTR1829 (www.trialregister.nl).

Information leaflet and prior consultation

Together with the invitation, all invitees received a leaflet with information on the CRC screening program in general, benefits and (complication) risks of colonoscopy or CT colonography (depending on the invitation) and on follow-up in case of a positive test result. Information leaflets were derived from previous CRC screening pilots and aimed at providing all invitees with information about the CRC screening program and the procedure itself, in order to facilitate informed decision-making on

participation. Both information leaflets, as well as the invitation letters, were written and reviewed by gastroenterologists, radiologists, nurses and experts from the comprehensive cancer centers. Further, the Dutch Health Council has scrutinized this material extensively prior to giving approval for this study.

Responding invitees received a standardized prior consultation with the research staff to inform them about the bowel preparation, the procedure itself and to check on contraindications and/or exclusion criteria. Invitees were excluded from participation when they had had a full colonic examination (colonoscopy, CT colonography or double barium contrast enema) in the previous five years, were scheduled for surveillance colonoscopy (personal history of CRC, adenomatous polyps or inflammatory bowel disease (IBD)) or when they had a severe or end-stage disease with a life expectancy of less than 5 years. In addition, CT colonography responders were excluded when they had been exposed to ionizing radiation for research purposes within the previous 12 months and when they had hyperthyroidism or iodine contrast allergy.

All responders who were willing to undergo screening signed written informed consent. They were scheduled for the screening procedure within four weeks after the prior consultation. Timing of the procedure was self-selected, but within a fixed screening timetable.

Colonoscopy

All colonoscopies were performed according to the standard quality indicators defined by the Society of Gastrointestinal Endoscopy(13). For bowel preparation, all participants started a low-fiber diet, two days before colonoscopy. Subsequently, all participants received 2L of polyethylene electrolyte glycol solution (Moviprep; Norgine bv, Amsterdam, The Netherlands) and 2L transparent fluid, split-dose or single dose, dependent on time of procedure (morning or afternoon).

All colonoscopies were performed by experienced gastroenterologists ($\geq$1000 colonoscopies). Forward viewing colonoscopes with variable stiffness were used (Olympus Medical Systems, Tokyo, Japan). Intravenous midazolam and fentanyl were administered if desired. Room air or carbon dioxide was used for insufflation, depending on screening location. Cecal intubation was achieved by changing positions (left lateral, right lateral, supine and prone position) during intubation if needed. At the discretion of the endoscopist, antispasmodic medication (butylscopolamine) was given intravenously at the start of withdrawal of the endoscope and repeated if necessary. After cecal intubation, colonic mucosa was carefully inspected during withdrawal for at least 6 minutes. Detected lesions were directly removed during the same procedure, whenever possible. If not, biopsies were obtained for histopathology.

Participants were informed about the colonoscopy findings on the day of the procedure. In case of polyps or cancer, participants were informed on the definitive diagnosis by telephone or at the outpatient clinic within two weeks, followed by further staging investigations and referral for further treatment. Advice regarding surveillance colonoscopy was given according to Dutch adenoma surveillance guidelines (CBO)(14)

CT colonography

Participants received a non-cathartic bowel preparation consisting of two times 50 mL of iodinated contrast agent (Telebrix Gastro, Guerbet, Aulnay sous Bois, France) on the day prior to CT colonography and 50 mL one-and-a-half hour before the examination, combined with a low-fiber diet for one day.(15;16) We used this preparation scheme as previous studies showed that the use of a non-cathartic preparation scheme with 200 mL of iodinated contrast resulted in high per-patient sensitivities for polyps ≥6mm of 90-98% and has the advantage that participants do not have to ingest four liters of fluid or use laxatives.(15;16) However, it does not prevent the development of diarrhea, as most iodinated contrast agents are hyperosmotic. Nowadays, non-cathartic bowel preparation for CT colonography consisting of fecal tagging with barium or iodine without laxatives is increasingly used.(17)

All CT colonography examinations were performed by experienced personnel. Colonic distension was obtained with an automatic CO_2 insufflator (PROTOCO2L, Bracco, EZEM, Lake Success, USA) after intravenous administration of 1 ml butylscopolamine or (when contraindicated) 1 mg of glucagonhydrochloride intravenously. When both spasmolytica were contra-indicated, no bowel relaxants were used. The aim was to insufflate three liters (1.3 left side, 0.9 supine and 0.8 right side) or at least two-and-a-half liters within a maximum insufflation time of 5 minutes before scanning. Images were obtained in both the supine and prone position, using a low dose scan protocol. All participants were informed by telephone about the CT colonography result within two weeks.

Participants with one or more CT colonography lesions ≥10mm were referred for follow-up colonoscopy within 3 weeks, during which CT colonography findings were revealed using segmental unblinding. All participants with 1-2 lesions of 6-9 mm were recommended to undergo surveillance CT colonography after 3 years; patients with ≥3 lesions in this range were recommended follow-up CT colonography after 1.5 years. Participants with relevant extracolonic findings were invited at the outpatient clinic and referred for corresponding follow-up.

Expected Burden Questionnaire (EBQ)

All invitees received a validated questionnaire by postal mail on the expected burden of the screening procedure (expected burden questionnaire, EBQ) within four weeks before the screening procedure. They were asked to complete the questionnaire prior to the screening procedure and to return it by mail in a prepaid envelop. All non-participants received the same questionnaire within four weeks after the initial invitation and were asked to return it by mail. The EBQ was based on previous Dutch FOBT screening pilots and on studies investigating the acceptance of CT colonography and patient perception of diagnostic tests for fecal incontinence.(18-21) With the EBQ we collected information on the expected embarrassment, pain and burden of the bowel preparation and the examination itself. All items were scored on a five-point Likert scale (1=not at all; 2=slightly; 3= somewhat; 4=rather; 5=extremely).(22) Completed EBQs were scanned and responses were automatically transferred to a database. The questionnaire also collected information on background characteristics like educational and income levels.

Perceived Burden Questionnaire (PBQ)

Participants received a second questionnaire by postal mail 14 days after the examination. At that point, participants had already been informed about the final result of the screening procedure. This second questionnaire addressed the perceived burden of the screening procedure (PBQ). Similar to the EBQ, the PBQ was based on previous CRC screening pilots and had been validated in previous screening cohorts. The PBQ contained items on perceived embarrassment, pain and burden of the bowel preparation, the examination itself and on the overall burden of the screening procedure In addition, the PBQ included specific items related to colonoscopy or CT colonography. All items were scored on a five-point Likert scale (1=not at all; 2=slightly; 3=somewhat; 4=rather; 5=extremely).(22)

With the questionnaire we also collected information on previous experience with colonoscopy or CT colonography, the most burdensome part of the colonoscopy or CT colonography (preparation, examination, abdominal symptoms afterwards, waiting for the results or sedation in case of colonoscopy) and the willingness to return in future screening rounds.

Participants were asked to fill in the questionnaire directly after receiving it and to send it back by mail in a pre-paid envelop. If participants did not respond, they were not reminded. In case of a positive CT colonography test result, a subject was asked individually to complete the PBQ prior to follow-up colonoscopy. Completed PBQs were scanned and responses were automatically transferred to a database.

Statistical analysis

Expected burden was compared between colonoscopy and CT colonography invitees: those who had been invited, regardless participation. All EBQs completed after the screening procedure were excluded from the analysis. Perceived burden was compared between actual colonoscopy and CT colonography participants. Items allowing a comparison between expected and perceived burden were analyzed using the Mann-Whitney test or chi-square statistics.

In addition, items specific for colonoscopy or for CT colonography were analyzed separately. We performed additional analyses to investigate the influence of a delayed return of PBQ on the perceived burden. SPSS version 18.0 for Windows (SPSS, Chicago, Ill) was used to perform all statistical tests.

RESULTS

The EBQ was returned by 2,111 colonoscopy invitees (36%) and 1,199 CT colonography invitees (41%). Forty-four EBQs (27 in colonoscopy arm and 17 in CT colonography arm) of screening participants had to be excluded because participants had completed the EBQ after the screening procedure. As shown in Figure 1, 1,276 colonoscopy invitees participated (22%), compared to 982 CT colonography invitees (34%). The PBQ was returned by 1,009 colonoscopy participants (79%) and by 801 CT colonography participants (82%). Background characteristics are summarized in **Table 1**.

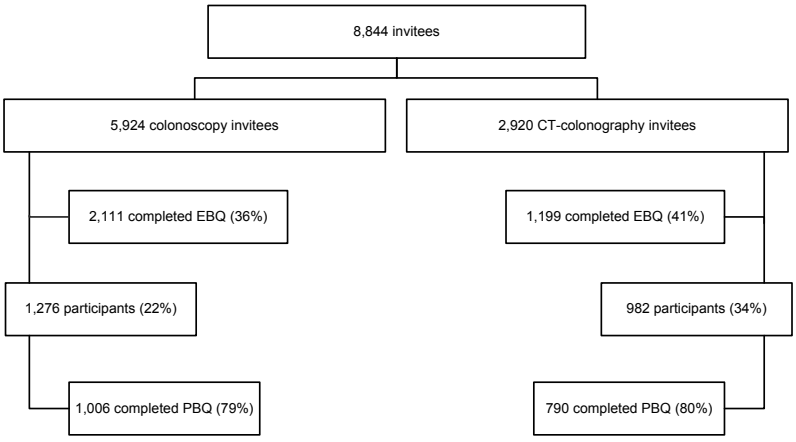

Figure 1: Overview of response to the expected and perceived burden questionnaire among invitees of a primary colonoscopy or CT colonography screening program.
Forty-four EBQs (27 in colonoscopy arm and 17 in CT colonography arm) were excluded as they were completed after the procedure
EBQ = Expected Burden Questionnaire; PBQ = Perceived Burden Questionnaire

Table 1: Respondents' baseline characteristics

	Invitees		Participants	
	Colonoscopy	**CTC**	**Colonoscopy**	**CTC**
	N=5,924	N=2,920	N=1,276	N=982
Respondents (n)	2,111 (36%)	1,199 (41%)	1,009 (79%)	801 (82%)
- Age in years (median, IQR)	60 (55-65)	60 (55-66)	60 (56-65)	60 (55-66)
- Gender (% male)	583 (49%)	1,015 (48%)	503 (50%)	406 (51%)
- Married/lived together (%)*	1,786 (85%)	990 (84%)	747 (87%)	654 (87%)
- Social economic status (mean, SD)**	3.2 (SD 1.4)	3.1 (SD 1.4)	3.2 (SD 1.4)	3.1 (SD 1.4)
- Education*				
- *Elementary (%)*	101 (5%)	65 (6%)	41 (5%)	27 (4%)
- *Secondary (%)*	1,418 (68%)	705 (60%)	621 (70%)	452 (60%)
- *Tertiary and postgraduate (%)*	530 (25%)	375 (32%)	212 (25%)	269 (36%)
- Prior endoscopy experience (%)*	N/A	N/A	138 (14%)	105 (13%)

***** As not all respondents completed the questions on their marital status, education and prior endoscopy experience, the percentages mentioned for these items are not based on the total number of respondents, but on the total number of invitees and participants who answered those questions.

****** Socio-economic status was categorized as very low, low, medium, high and very high (1-5).

Expected burden invitees

Figure 2 summarizes the results on expected burden, including (pooled) standard deviations. Twenty-seven percent of colonoscopy invitees expressed to be extremely reluctant to undergo screening compared to 6% of CT colonography invitees (overall mean score 3.3 versus 2.4; p<0.001).

Bowel preparation:

A smaller proportion of responding colonoscopy invitees than CT colonography invitees expected to be not or only slightly embarrassed by drinking the bowel preparation (64% versus 77%; 2.2 versus 1.8; p<0.001). A majority of CT colonography invitees expected that drinking the bowel preparation would be not or only slightly painful, more than in colonoscopy invitees (79% versus 61%; 1.9 versus 2.4; p<0.001). Thirty-four percent of colonoscopy invitees expected that drinking the bowel preparation would be rather or very burdensome compared to 10% of CT colonography invitees (3.0 versus 2.3; p<0.001).

Examination itself:

A larger proportion of colonoscopy invitees expected to be somewhat, rather or extremely embarrassed by undergoing the screening procedure (44% versus 24%; 2.5 versus 1.9; p<0.001). Only 5% of colonoscopy invitees expected that the screening

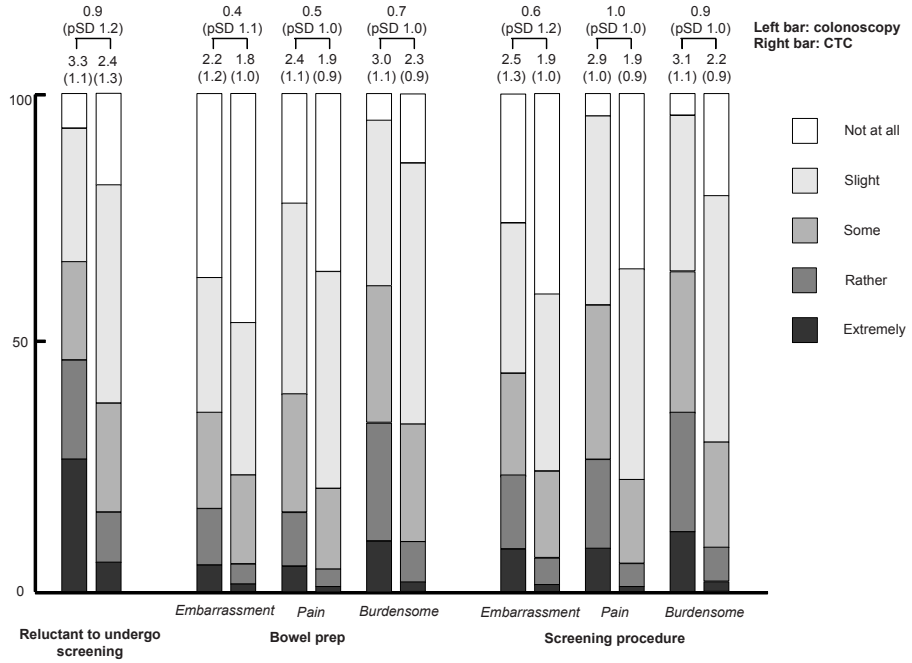

Figure 2: Reluctance to undergo screening and expected embarrassment, pain and burden of bowel prep and screening procedure.
On top of the bars, mean scores, standard deviations (between parantheses), differences in mean scores and pooled standard deviations (pSD) are displayed. All items differed significantly between colonoscopy and CT colonography (p<0.001).

procedure would not be painful compared to 35% of CT colonography invitees (2.9 versus 1.9; p<0.001). Colonoscopy invitees expected the screening procedure to be more burdensome than CT colonography invitees (rather or extremely burdensome; 36% versus 9%, 3.1 versus 2.2: p<0.001).

Perceived burden participants

Figure 3 summarizes the findings with the perceived burden questionnaire, including (pooled) standard deviations.

Bowel preparation:

Drinking the preparation was more often perceived as not or only slightly burdensome by CT colonography participants (39% versus 84%; overall mean score 3.0 versus 1.7; p<0.001), while colonoscopy participants perceived the related bowel movements more often as not burdensome (36% versus 27%; 2.0 versus 2.2; p<0.001) and not embarrassing (72% versus 62%; 1.4 versus 1.6; p<0.001). The perceived pain of the related bowel movements was not significantly different (1.4 versus 1.5; p=0.06).

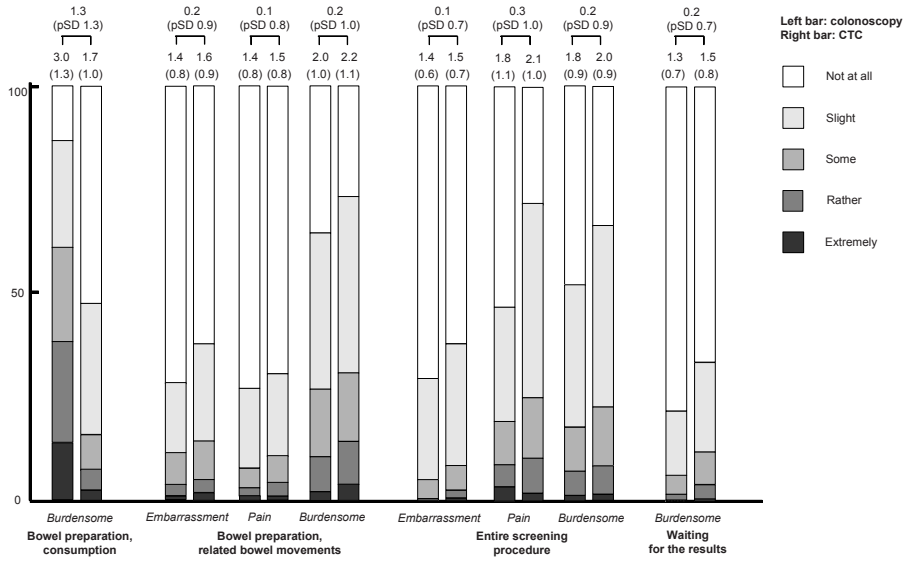

Figure 3: Perceived burden of colonoscopy and CT colonography.
On top of the bars, mean scores, standard deviations (between parantheses), differences in mean scores and pooled standard deviations (pSD) are displayed. All items differed significantly between colonoscopy and CT colonography ($p<0.001$), except for experienced pain caused by the bowel movements (related to the preparation), which was not significantly different between colonoscopy and CT colonography ($p=0.06$).

Waiting for the results:

Colonoscopy participants perceived waiting for the results, more often as not burdensome than CT colonography participants (78% versus 66%; 1.3 versus 1.5; $p<0.001$).

Physical health around the examination:

On the day prior to the examination, 48% of colonoscopy participants and 37% of CT colonography participants were hindered in their normal activities ($p<0.001$), while CT colonography participants were hindered more often the day after the examination (15% versus 31%, $p<0.001$). Prior to the examination, colonoscopy participants more often experienced trouble sleeping (31% versus 24%, $p=0.001$), while CT colonography participants experienced this more often afterwards (6% versus 12%, $p<0.001$).

Abdominal complaints after the examination (more than normal) were experienced less often by colonoscopy participants (24% versus 48%, $p<0.001$), but if experienced, these abdominal complaints were perceived as more painful by colonoscopy participants (somewhat, rather or extremely painful: 40% versus 28%, $p=0.01$). The abdominal complaints were rated as not burdensome by 19% of colonoscopy participants versus 9% of CT colonography participants ($p<0.05$).

Entire screening procedure:

Colonoscopy participants rated the entire screening procedure more often as not or only slightly embarrassing (95% versus 92%; overall mean score 1.4 versus 1.5; p<0.001), more often as not painful (53% versus 28%; 1.8 versus 2.1; p<0.001) and more often as not burdensome (48% versus 34%; 1.8 versus 2.0; p<0.001). The majority of colonoscopy participants (73%) scored the bowel preparation as most burdensome aspect of the overall screening procedure, while CT colonography participants scored the examination itself (37%) or the bowel preparation (32%) as most burdensome aspects.

The entire screening procedure turned out worse than expected by 12% of colonoscopy participants and by 21% of CT colonography participants, experienced as expected by 13% and 20%, and turned out better than expected by 75% and 59%, respectively (p mean score<0.001).

Perceived burden colonoscopy related items

Of all colonoscopy participants 88% received sedation. Insertion of the endoscope into the rectum was perceived as not or slightly burdensome by 92% of colonoscopy participants, as not or slightly embarrassing by 93% and as not or only slightly painful by 89%. The rest of the examination, including cecal intubation and withdrawal of the colonoscope, was experienced as not or only slightly burdensome by 90%. It was scored as not or only slightly embarrassing by 98% and experienced as somewhat, rather or extremely painful by only 17%. Of those participants that received sedation, 98% scored recovering after colonoscopy as not or only slightly burdensome.

Perceived burden CT colonography related items

Of all CT colonography participants, 92% experienced diarrhea; in 37% of participants diarrhea had started after ingestion of 50mL of Telebrix, in 47% after 100mL and the remaining 16% of participants experienced it after ≥150mL. Insertion of the rectal catheter was experienced as not at all or slightly burdensome by 90% of participants. Insufflation of CO_2 was experienced as rather or extremely painful by 23% of participants and was rated as rather or extremely burdensome by 20% of participants. Changing positions during the procedure was scored as not or only slightly burdensome by 81% of participants.

Future screening rounds

Ninety-six percent of colonoscopy participants would recommend others to undergo screening compared to 95% of CT colonography participants. Ninety-six of colonoscopy and 93% of CT colonography participants would probably or definitely participate in a next screening round (p for mean score=0.99).

Influence of delayed return on perceived burden

The PBQ was returned within 4 weeks after the screening procedure by 45% of colonoscopy responders and by 67% of CT colonography responders, after 6 weeks these percentages were 72% and 82% respectively. CT colonography participants returned their PBQ more quickly, after a median of 22 days (IQR 18-31) versus 29 days in the colonoscopy group (IQR 20-42); $p<0.001$). In the analyses to investigate the influence of delayed return of PBQ, we found results comparable to those of the main analysis (data not shown).

DISCUSSION

In this study we compared the expected and perceived burden of primary colonoscopy and CT colonography screening in a randomized population-based screening program. The expected burden among responding colonoscopy invitees was significantly higher than in CT colonography invitees. In contrast, the perceived burden of the entire screening procedure was evaluated as significantly higher in CT colonography participants than in colonoscopy participants. Nevertheless, the level of intended participation in a next screening round was very much comparable in both groups.

Our study has several strengths. Subjects had been randomly invited for primary population-based CRC screening using either colonoscopy or CT colonography making a head-to-head comparison possible. Previous studies compared both screening methods in a tandem design, in which subjects underwent a colonoscopy after a CT colonography or vice versa. Invitees were not allowed to switch between both strategies, preventing the possibility of a selection bias. The information leaflets for colonoscopy and CT colonography invitees were identically designed, both written and reviewed by gastroenterologists, radiologists, nurses and experts from the comprehensive cancer centers, and aimed at providing decision relevant knowledge. Further, the invitation material was approved by the Dutch Health Council. All participants received a standardized prior consultation to inform them about the entire screening procedure, including the bowel preparation. Both questionnaires had been validated in previous CRC screening pilots. Almost 80% of participants returned their PBQ, a very reassuring response rate.

A number of potential limitations should also be acknowledged. The lower participation rate in the colonoscopy screening group (22% versus 34%) should be kept in mind when interpreting the results. Participation can be expected to be influenced by the expected burden. A larger proportion of CT colonography participants than colonoscopy participants indicated that the screening procedure turned out worse than expected (21% versus 12%). This suggests that CT colonography invitees may have

been more inclined towards participation, because they might have underestimated the burden of CT colonography.

Although all participants received the PBQ two weeks after the procedure, colonoscopy participants were more likely to return their questionnaire at a later stage compared to CT colonography participants. This difference may have affected the perceived burden scores, as perceived burden has been suggested to increase over time.(19;23) In our additional analyses however, which included the PBQs returned within 4 and within 6 weeks after the procedure, we observed comparable results, which suggest that our main findings were not affected by the delay in responding. As not all participants returned their PBQ, we must consider the possibility of a selective response but the number of participants who returned the PBQ was equally high in both arms, suggesting that comparisons are valid.

Although most of the differences between CT colonography and colonoscopy participants were statistically significant, the actual differences were sometimes small when evaluated relative to the variability within groups. In our study, for example, perceived burden scores of the entire screening procedure were 1.8 for colonoscopy and 2.0 for CT colonography. This difference of 0.2 on the five-point scale was highly significant ($p<0.001$) but the pooled standard deviation (SD) of the scores was 0.9, indicating a large within-group variability in scores. Norman et al. suggested to indicate clinically important differences as those above approximately half a standard deviation (SD).(24) This remark does not concern our results on expected burden as differences between mean scores were all larger than a half pooled SD.

We anticipated that a lower experienced burden would be associated with a higher willingness to participate in future screening rounds. This was not observed in our study, where the overwhelming majority of participants in both groups indicated they would participate in a next screening round and would recommend undergoing screening to others.

To our knowledge, no previous randomized controlled trials have been published comparing the expected burden of colonoscopy and CT colonography. One small Australian (population-based) randomized screening study reported on perceived burden of six different screening strategies including colonoscopy and CT colonography. This study showed higher pain and embarrassment scores in the CT colonography group (n=38 participants) than in the colonoscopy group (n=63 participants).(25) As far as we know, other studies comparing the perceived burden of both techniques used non-randomized tandem designs and were therefore not comparable to our study.(7;8;26)

We observed that drinking the bowel preparation was experienced as more burdensome in the colonoscopy arm than in CT colonography participants. This can be attributed to the higher intake of fluid before colonoscopy, compared to the limited

bowel preparation in CT colonography. A high amount of fluid intake is a persistent burdensome aspect in colonoscopy. Switching to a more limited bowel preparation, such as sodiumpicosulfate, may reduce the burden in the future.(27) However, additional intake of a substantial amount of clear fluid will still be necessary, comparable to polyethylene glycol, which was used in our study. In contrast, the related bowel movements were experienced as more burdensome in CT colonography. Possibly, these complaints were not anticipated by CT colonography participants.

In our study CT colonography participants reported more often abdominal complaints after the procedure, although colonoscopy participants experienced the associated pain as more burdensome. The larger proportion of CT colonography participants experiencing abdominal complaints could be explained by the lower expected burden or attributed to post-procedural diarrhea, caused by the tagging agent. Based on these findings, one may consider the use of non-ionic contrast agents in order to minimize the amount of related bowel movements, post-procedural diarrhea and other post-procedural abdominal complaints. However further studies are needed to evaluate whether non-ionic contrast agents will result in similar tagging quality for CT colonography, compared to ionic contrast agents. We aimed for homogeneous tagging and therefore did not choose barium only tagging. Bowel preparation with a combination of barium and iodine or lower doses of iodine has been proposed which may be a good compromise between homogeneous tagging and side effects.(8;28)

Abdominal complaints were experienced as more painful by colonoscopy participants. This might be explained by the fact that colonic distention during CT colonography was achieved using CO_2, while colonic distention during colonoscopy was achieved using room air or CO_2. One previous randomized trial showed a reduction in patient discomfort using CO_2 for insufflation instead of room air during colonoscopy, as CO_2 is rapidly absorbed from the colon which probably results in fewer abdominal cramps.(29) Using only CO_2 instead of using also room air may decrease the experienced post-procedural abdominal pain in colonoscopy screening.

To our surprise, CT colonography participants assigned higher burden scores to the entire examination than colonoscopy participants. It is likely that the higher perceived burden in CT colonography was also influenced by the relatively lower expected burden, as the examination turned out better than expected in 75% of the colonoscopy participants compared to 60% of CT colonography participants. An explanation for this difference might be that CT colonography invitees more often underestimated burdensome elements of CT colonography, such as the watery diarrhea caused by the intake of iodinated contrast agents, or the bowel cramps occurring after insufflations of 2.5 to 3.0 liters of CO_2 for achieving sufficient bowel distention. In addition, the use of sedation could be responsible for the lower experienced burden in colonoscopy, as this could lead to retrograde amnesia. Sedation is not common practice in CT colonog-

raphy, as so far the advantages did not seem to outweigh the disadvantages, such as recovery time, restrictions on driving and additional costs.

Our information leaflets were identically designed and aimed at disseminating adequate decision-relevant information to all invitees. All participants received a standardized prior consultation to inform them about the entire screening procedure itself and the bowel preparation. Despite our efforts to inform all participants adequately, it is still possible that not all had a similar understanding of the procedure. Future efforts could target improvements in information leaflets and the development of campaigns to increase appropriate awareness of all potentially burdensome aspects in CT colonography. The fact that colonoscopy participants were informed about the temporary result directly after the procedure, while CT colonography participants received their results after two weeks, may be a third explanation for the difference in perceived burden. We observed that waiting for the test results was perceived more burdensome by CT colonography participants, suggesting that providing a temporary CT colonography result on the day of the examination could contribute to a lower perceived burden of CT colonography.

A priori, based on studies in high-risk participants, we anticipated CT colonography to be less burdensome than colonoscopy, making CT colonography a good option for CRC screening.(30) Our study, performed in an average risk population, showed that the entire screening procedure was experienced as more burdensome by CT colonography participants than by colonoscopy participants. This finding may attenuate some of the potential perceived advantages of CT colonography compared to colonoscopy in a screening setting. At the same time, it is reassuring that in both groups the majority of the patients experienced the screening procedure as not or only slightly burdensome and that there was no difference between the groups in intended participation in a next screening round.

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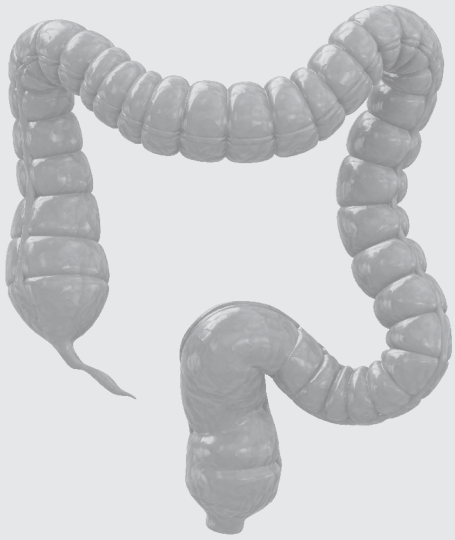
CHAPTER 4

The Colonoscopy Unit Costs of Population-based Screening for Colorectal Cancer



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Submitted

ABSTRACT

Background: Cost-effectiveness analyses of colorectal cancer screening generally base colonoscopy costs on reimbursement rates. However, these rates poorly reflect true costs in a screening setting. We therefore assessed true costs of colonoscopy screening in practice.

Methods: 6,600 screening-naïve subjects aged 50-75 years were invited for colonoscopy, of which 1426 (22%) attended. Procedure times, personnel and equipment were registered. Costs were specified for personnel and other costs. Costs for alternative scenarios, such as screening by endoscopy nurses were also determined.

All authors have had access to the study data and have reviewed and approved the final manuscript.

Results: The median duration of a procedure in a dedicated setting was 18:29 minutes (SD 07:08); allowing for scheduling 15 colonoscopies per day. Total costs of screening colonoscopy averaged at €252, being €184 for negative colonoscopy, versus €323 for colonoscopy requiring polypectomy. Total average costs increased to €252 if the screening program was extended into evening hours and decreased to €206 with nurse endoscopists. Procedure intake costed an additional €12.79.

Conclusion: The average costs per colonoscopy in a dedicated screening setting are considerably less than current reimbursement rates for clinical colonoscopy. www.trialregister.nl, NTR1829.

BACKGROUND

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality in the Western world, with an estimated 500 000 annual deaths. (5, 47, 48) An effective population-based screening program can lower mortality and morbidity rates for this cancer. (5) Several such screening strategies have been proposed, and the decisions to implement one strategy rather than the other should be guided by data on the associated costs and the resulting effectiveness.

Colonoscopy is regarded as the most accurate screening modality. A number of economic analyses have been performed to estimate the cost-effectiveness of primary colonoscopy screening. (38-40, 49, 50) In these analyses colonoscopy costs were generally based on clinical reimbursements, based on routine patient care. These estimates may not be representative of the actual costs for screening colonoscopies. Screening costs were most likely overestimated, presuming that costs for one colonoscopy in a dedicated high throughput screening setting are lower than the costs for a regular colonoscopy in a clinical setting. Analyses estimating the true unit costs in a population-based screening program, using colonoscopy as a primary screening method are lacking.

Not only the procedure itself, but different other aspects have to be evaluated to calculate the real costs for a screening colonoscopy in a dedicated screening setting. In an invitational setting, a specialized screening organization is necessary to coordinate the invitational process, mailings and correspondence regarding test results. Furthermore, screenees have to be informed about the advantages and disadvantages of screening, to consider benefits and harms of screening enabling informed decision. Besides, information on a person's general health, co-morbidities and medication must be obtained prior to the screening colonoscopy. An explanation regarding bowel prep is necessary to improve the quality of the examination and to minimize the number of re-exams because of insufficient bowel preparation.

Despite these factors, there are several reasons why a screening colonoscopy may be less expensive than a regular clinical colonoscopy. First of all, in screening, most participants will have no abnormalities, or only adenomas, found during colonoscopy. Second, a dedicated screening setting will most likely be established as an efficient high through-put endoscopy centre. Finally, when colonoscopy is the primary screening method in population-based screening, possible discounts can be expected on materials and investments as well as full capacity on investments.

The aim of this study was to determine the true costs for screening colonoscopy in a dedicated screening setting.

METHODS

In the COCOS (COlonoscopy or COlonography for Screening) trial, a random selection of the general Dutch population (n=6600), aged 50-75 years, in the regions Amsterdam and Rotterdam were invited for colonoscopy screening. (51) All invitees were screening-naïve, average risk individuals. They were invited between June 2009 and July 2010 by two Regional Cancer Screening Centers. Included with the invitation was an information leaflet on CRC in general, the advantages and disadvantages of screening, possible risks, and the need for follow-up in case of a positive test result. Invitees who were willing to participate had a pre-colonoscopy assessment with the research staff. The overall design of the COCOS trial has been described in detail, elsewhere (31), as well as the primary outcome measures: participation rate and diagnostic yield (51). Ethical approval was obtained from the Dutch Health Council (2009/03WBO, The Hague, The Netherlands). The trial was included in the Dutch trial register prior to its initiation: NTR1829 (www.trialregister.nl). All authors have had access to the study data and have reviewed and approved the final manuscript.

Costs at the screening organization

Cost components for the invitational process included sending the invitation letter and a reminder in case of non-response, confirmation of the colonoscopy appointment, and communication of the results (such as printing costs of the information leaflets and postal charges). The average personnel and overhead costs were calculated based on the total personnel costs and overhead costs made by the screening organizations during the screening trial.

Colonoscopy

Colonoscopies were performed in two centers in Amsterdam and Rotterdam by experienced gastroenterologists (≥1000 colonoscopies) according to the standard quality indicators defined by the American Society for Gastrointestinal Endoscopy (52) and the European guideline for quality assurance in screening colonoscopy. (53)

For bowel preparation, we used 2 litres of polyethylene electrolyte glycol solution (Moviprep; Norgine bv, Amsterdam, The Netherlands) together with 2 litres of transparent fluid for 2 days. A low-fiber diet was recommended. The quality of the bowel preparation was scored by the colonoscopist using the validated Ottawa score. (54)

Conscious sedation (midazolam) and analgesics (fentanyl) were administered intravenously at the discretion of the participant and the endoscopist. Use and dosages of sedatives and analgesics as well as butylscopolamine were registered per participant. The total procedure time and withdrawal time were measured. The recommended minimum withdrawal-time was 6 minutes. Size and morphology of all lesions were

registered and all lesions were removed immediately if possible. Materials used for polypectomy and biopsy sampling were registered per procedure. In case of inadequate bowel preparation, the colonoscopy was interrupted and rescheduled.

For fifty percent of colonoscopies, *a dedicated screening setting* was mimicked. The rest of the colonoscopies were performed in the normal clinical setting, which will be called *non-dedicated screening setting*.

Description of the dedicated screening setting

After registration by the receptionist, a nurse accompanied screening participants to recovery room where they were prepared for the colonoscopy. The recovery was also used as a preparation room, so that one nurse could take care of participants, before and after the colonoscopy.

The nurse placed an infusion catheter for administration of sedatives and analgesics during colonoscopy. In the examination room, one gastroenterologist and one nurse were performing the colonoscopies. Procedure times were recorded. Time interval in between two procedures was calculated based on the total operational time diminished by total examination time, resulting in approximately 10 minutes. The *dedicated screening setting* was considered the base-case.

Description of the non-dedicated screening setting

In the non-dedicated screening setting, colonoscopies were performed in a regular clinical setting. Times were not measured in this setting. In accordance with the routine time-slots accounted for per colonoscopy in this setting, procedure time was set at 30 minutes and time between two colonoscopies at 15 minutes.

Costs

Unit costs were calculated for a positive (PCol) and negative screening procedure (NCol) in both screening settings. The ratio of PCol's and NCol's was used to calculate the average costs per screening procedure. A positive screening procedure was defined as a colonoscopy with at least one biopsy or polypectomy, regardless of histology results. One screening procedure was defined as a single primary screening colonoscopy without surveillance or follow-up.

Costs were updated for 2011 and divided into personnel, material, investments, and overhead costs for I) the invitation and scheduling process, II) the pre-colonoscopy assessment, III) the colonoscopy including aftercare, IV) correspondence of the final test results. We report all costs in euros (€) for the year 2011. Personnel costs were calculated, using the salary schemes of hospitals in the Netherlands.

Costs for non-participants, non-responders and drop-outs were calculated separately. A non-responder was considered an individual who had not responded after

an invitation and a subsequent reminder letter. A non-participant was considered an invitee who indicated not to participate after receiving an invitation letter. Finally, a drop-out was considered a screening invitee who decided not to attend colonoscopy after the pre-colonoscopy assessment.

A workday was considered to consist of 7.5 working hours (8 hours minus 30 minutes lunch break). The number of working days per year was set at 234 days per fulltime-equivalent. The number of screening colonoscopies which could be performed per day in a *dedicated screening setting* was calculated by dividing 7.5 hours by the average examination time of colonoscopies performed in this setting. The number of screening colonoscopies per day in *a non-dedicated screening setting* was calculated in the same way.

For every participant, time spent in the recovery room was recorded. The average time spent at the recovery room was used to calculate the number of beds that were needed in both screening settings. The longest time spent at the recovery was used to calculate the number of beds needed in a worst case scenario. Eight square meters were needed to place one bed.

Two expert pathologists, one in each center, assessed all tissue samples. For every PCol, time needed to assess all samples per PCol was registered. The average assessment time per PCol was calculated. Salary costs were accounted for the actual assessment time.

Finally, costs for a telephone consultation with a general practitioner were calculated, using the percentage of participants who, according to the Dutch national post-polypectomy guidelines (55), received a surveillance advice multiplied by the unit costs for reporting the final test results by telephone. Costs for a face-to-face consultation were calculated in case of detection of colorectal cancer. For each setting, overhead costs were calculated as 42% of personnel plus material costs. (56)

Scenarios

The costs were calculated for the following colonoscopy screening scenarios:

1. *A dedicated screening setting (base case).*
2. *A non-dedicated screening setting with 10 colonoscopies per day (instead of 15).*
3. *A pre-colonoscopy assessment using a questionnaire in combination with an information leaflet by postal mail (instead of a consultation by telephone).*
4. *Screening colonoscopies performed by an endoscopy nurse (instead of a gastroenterologist).*
5. *Screening colonoscopies performed also during evening hours (instead of only during regular office hours).*
6. *Colonoscopies performed with or without the use of sedation.*

RESULTS

Between June 2009 and August 2010, 6600 persons were invited for colonoscopy screening.

(Figure 1) A total of 1616/6600 (24%) subjects attended a pre-colonoscopy assessment. Subsequently, 1426 subjects attended colonoscopy, being 22% of all invitees and 88% of those undergoing a pre-colonoscopy assessment. The 190 participants that after the pre-colonoscopy assessment decided not to attend colonoscopy did so for many different reasons. In 698 (49%) colonoscopies, at least one biopsy or polypectomy was performed; these were classified as *positive screening colonoscopies (PCol).* In total, a number of 1794 tissue samples were taken. Of these 698 participants with a positive colonoscopy, 128 participants had an advanced adenoma (18%). Histopathology of the tissue samples is listed in Table 1.

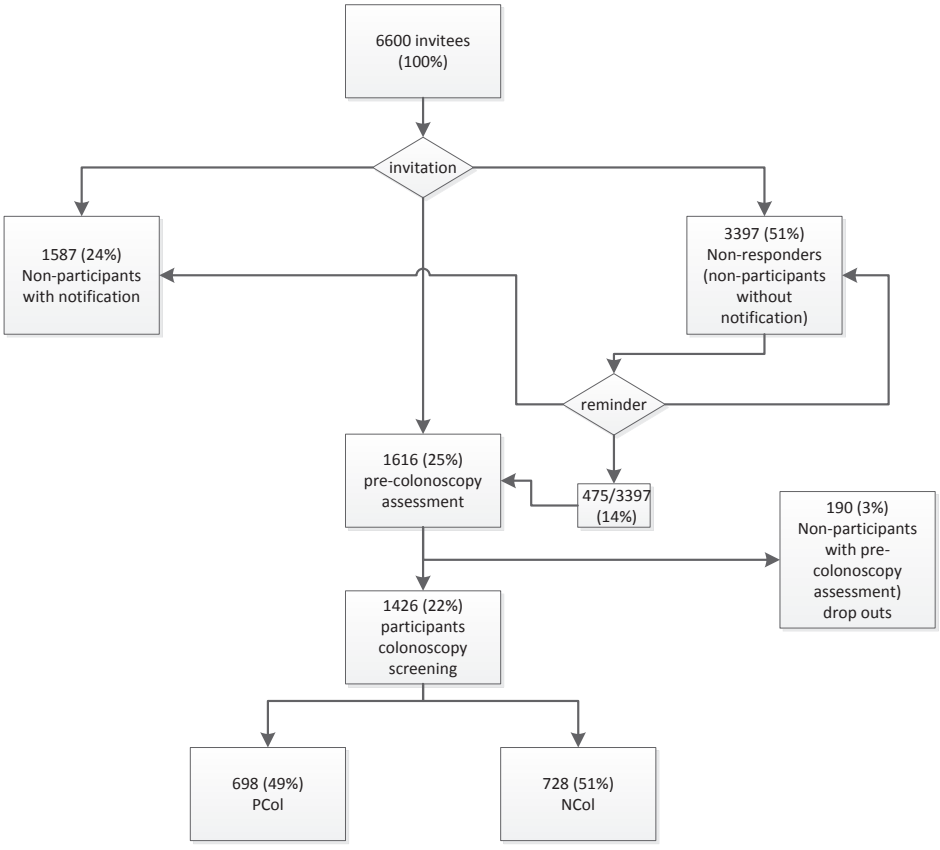

Figure 1: Study flowchart

Table 1: Total yield of 698/1426 (49%) positive screening colonoscopies

Histology	n
Carcinomas	9
Adenomas	777
Villous	2
Tubulovillous	83
Tubular	675
Serrated adenomas	112
Hyperplastic polyps	633
Inflammatory polyps	8
Juvenile polyps	2
Lipomas	3
Colorectal mucosa	205
Tissue sample lost or too small to examine	33
Missing	12
Total number of tissue samples	**1794**

A snare was used in 51% of polypectomies, a biopsy forceps in 41% and a hot biopsy in 6% of cases. Total yield for the positive screening procedures is listed in Table 1. Colonoscopy was incomplete in 39 (3%) participants for different reasons. The procedure was successfully repeated in 11 participants, 28 declined re-examination.

Scenario 1: *Dedicated screening setting (15 colonoscopies per day) (base case) (Table 2)*

Costs for non-responders, non-participants and drop-outs

Numbers of non-responders, non-participants and drop-outs in the study are displayed in Figure 1. Invitational costs for a non-responder and a non-participant were €5.57 and €4.99 respectively. Costs for a drop-out were €17.78.

Costs in participants

In participants, next to the costs of the invitation (€4.99), there are the costs of the intake (€12.79 in the base case) and the costs of the colonoscopy procedure itself (Table 2). Concerning the latter, the following observations and calculations were made.

A dedicated screening setting was established for 712/1426 (50%) colonoscopies. The average examination time in this dedicated screening setting was 18:29 minutes (SD 07:08). The average examination time for a positive screening colonoscopy was 21:19 minutes (SD 07:29) versus 16:27 minutes (SD 06:08) for a negative screening colonoscopy. Based on a colonoscopy-screening unit consisting of one examination

Table 2: Costs per invitation, intake procedure and colonoscopy in a dedicated setting (base-case), a non-dedicated setting and other alternative scenarios (without reminder costs)

items	Dedicated screening setting (base case)	Non-dedicated screening setting (10 colonoscopies per day instead of 15)	Questionnaire instead of a pre-colonoscopy assessment	Nurse Instead of gastro-enterologist	Also during evening hours instead of only during daytime	Colonoscopy without Sedation instead of with sedation
Invitation procedure						
Personnel	*€1.53*	*BC*	*No scheduling appointment: -€1.53*	*BC*	*BC*	*BC*
Material	*€3.46*	*BC*	*BC*	*BC*	*BC*	*BC*
Subtotal invitation	***€4.99***	*BC*	***€3.46***	*BC*	*BC*	*BC*
Intake and scheduling appointment						
Personnel	*€9.29*	*BC*	*intake in 25% of cases: -€5.88* ***=€3.41***	*BC*	*BC*	*BC*
Material	*€3.50*	*BC*	*BC*	*BC*	*BC*	*BC*
Subtotal intake	**€12.79**	*BC*	***€6.91***	*BC*	*BC*	*BC*
Colonoscopy						
Personnel PCol	*€107.65*	*Less colonoscopies per year: €107.65 + €42.86 =* ***€150.51***	*BC*	*Nurse instead of gastro-enterologist: €107.65-€33.85=* ***€73.80***	*An extended program with 3 extra hours in the evening: €107.65+€3.67=* ***€111.32***	*Nurse recovery is needed for 50% only: €107.65- €7.44=* ***€100.21***

*Base-case (the dedicated screening setting (15 colonoscopies per day))

**These are the costs for a weighed average (51%/49%) for positive and negative colonoscopies based on the findings in the COCOS trial.

Table 2: Costs per invitation, intake procedure and colonoscopy in a dedicated setting (base-case), a non-dedicated setting and other alternative scenarios (without reminder costs)

Personnel NCol	*€88.74*	*Less colonoscopies per year: €88.74 + €27.16 =* ***€115.90***	*BC*	*Nurse instead of gastro-enterologist: €88.74-€27.87=* ***€60.87***	*An extended program with 3 extra hours in the evening: €88.74+€4.12=* ***€92.86***	*Nurse recovery is needed for 50% only: €88.74- €6.12=* ***€82.62***
Material PCol	*€44.51*	*Working clothes, washing and purchase: €44.51+€0.23 =* ***€44.74***	*BC*	*3 pairs of gloves and 3 uniforms instead of two: gloves + €0.06 uniforms + €0.13 €44.51+€0.19 =* ***€44.70***	*BC*	*No midazolam+ or anexate needed: €44.51 - €1.55=* ***€42.96***
Material NCol	*€28.21*	*Working clothes, washing and purchase: €28.21+€0.23 =* ***€28.44***	*BC*	*3 pairs of gloves and 3 uniforms instead of two: gloves + €0.06 uniforms + €0.13 €28.21+€0.19 =* ***€28.40***	*BC*	*No midazolam+ NaCl or anexate needed: €28.21-€1.55 =* ***€26.66***
Investments PCol	*€14.10*	*Less colonoscopies per year and 2 colonoscopes instead of 3: €14.10+€3.49 =* ***€17.59***	*BC*	*BC*	*More colonoscopies per year(4914 instead of 3510) €14.10-€4.38=* ***€9.72***	*2 beds needed at the recovery instead of three: €0.36-€0.14= €0.22 and no pulse-oximeters-€0.37 €14.10-€0.51 =* ***€13.59***

*Base-case (the dedicated screening setting (15 colonoscopies per day))

**These are the costs for a weighed average (51%/49%) for positive and negative colonoscopies based on the findings in the COCOS trial.

Table 2: Costs per invitation, intake procedure and colonoscopy in a dedicated setting (base-case), a non-dedicated setting and other alternative scenarios (without reminder costs)

Investments NCol	*€12.19*	*Less colonoscopies per year and 2 colonoscopes instead of 3: €12.19+€2.83 =* ***€15.02***	*BC*	*BC*	*More colonoscopies per year(4914 instead of 3510) €12.19-€3.57=* ***€8.62***	*2 beds needed at the recovery instead of three: €0.36-€0.14= €0.22 and no pulse-oximeter-€0.37 €12.19-€0.51 =* ***€11.68***
Recovery room	*€65.40 per m²/24 m² needed/3510 = €0.45*	*Less colonoscopies per year: €0.45+€0.22= €0.67*	*BC*	*BC*	*More colonoscopies per year (4914 instead of 3510): €0.45-€0.13 =* ***€0.32***	*Only 10 m² recovery needed instead of 24 m²: €0.45-€0.26=* ***€0.19***
Overhead PCol	*€70.02*	*€89.67*	*BC*	*€55.88*	*€69.67*	*€65.92*
Overhead NCol	*€54.20*	*€67.21*		*€42.80*	*€54.60*	*€50.88*
Subtotal PCol	***€236.72***	***€303.18***	***BC***	***€188.93***	***€235.53***	***€222.87***
Subtotal NCol	***€183.25***	***€227.24***	***BC***	***€144.71***	***€184.61***	***€172.03***
Pathological assessment only for PCol						
Personnel	*€39.95*	*BC*	*BC*	*BC*	*BC*	*BC*
Non-personnel	*€19.16*	*BC*	*BC*	*BC*	*BC*	*BC*
Overhead (42%)	*€18.99*	*BC*	*BC*	*BC*	*BC*	*BC*
Subtotal PCol	***€78.10***	***BC***	***BC***	***BC***	***BC***	***BC***

*Base-case (the dedicated screening setting (15 colonoscopies per day))

**These are the costs for a weighed average (51%/49%) for positive and negative colonoscopies based on the findings in the COCOS trial.

Table 2: Costs per invitation, intake procedure and colonoscopy in a dedicated setting (base-case), a non-dedicated setting and other alternative scenarios (without reminder costs)

Communication of final test results						
Personnel PCol	€6.98	*BC*	*BC*	*BC*	*BC*	*BC*
Personnel NCol	€0.00	*BC*	*BC*	*BC*	*BC*	*BC*
Non-personnel PCol	€1.16	*BC*	*BC*	*BC*	*BC*	*BC*
Non-personnel NCol	€1.16	*BC*	*BC*	*BC*	*BC*	*BC*
Subtotal PCol	***€8.14***	***BC***	***BC***	***BC***	***BC***	***BC***
Subtotal NCol	***€1.16***	***BC***	***BC***	***BC***	***BC***	***BC***
Total PCol	***€322.96***	***€389.42***	***BC***	***€275.17***	***€321.77***	***€309.11***
Total NCol	***€184.41***	***€228.40***	***BC***	***€145.87***	***€185.77***	***€173.19***
Total Pcol (including intake	€335.75	***€402.21***	***€329.87***	**€287.96**	**€334.56**	**€321.90**
Total Ncol (including intake	***€197.20***	***€241.19***	***€191.32***	***€158.66***	***€198.56***	***€185.98***
Total costs one colonoscopy**	**€252.30**	**€307.30**	**BC**	**€206.31**	**€252.41**	**€239.79**
Total costs one colonoscopy (including intake)**	**€265.09**	**€320.10**	**€259.21**	**€222.02**	**€265.20**	**€252.58**

*Base-case (the dedicated screening setting (15 colonoscopies per day))

**These are the costs for a weighed average (51%/49%) for positive and negative colonoscopies based on the findings in the COCOS trial.

room and one endoscopy team, an eight-hour workday, 10 minutes interval in between procedures and 30 minutes lunchtime, 15 colonoscopies were performed per day. Based on the assumption of 234 workable days per year, 3,510 colonoscopies could be performed per annum. Total costs per PCol in this dedicated screening setting were €322.96 and per NCol €184.41, accounting for the observed 51% PCol this resulted in an average cost of €252.30 per colonoscopy (Table 2). Seventy-four percent of these consisted of personnel and non-overhead costs.

Alternative scenarios

Some differences between scenarios affect the invitational costs, others the colonoscopy costs (Table 2).

Scenario 2: Non-dedicated screening setting (10 colonoscopies per day) - If instead of 15 only 10 colonoscopies could be performed per day, total average costs per colonoscopy (without the invitational costs and again based on 51% positive colonoscopies) increased to €307.30.

Scenario 3: Using a questionnaire for pre-colonoscopy assessment - When assuming that not all (base case) but only (potential) participants with diabetes, use of anticoagulants and/or a complete bowel examination in the previous five years would need an interactive pre colonoscopy assessment, 25% of our screening population would need a pre-colonoscopy assessment by telephone (source: COCOS trial (51)). In this scenario, a questionnaire-based pre-assessment sufficed for 75% of participants. The costs for the intake procedure in this scenario decreased to €6.91. (Table 2)

Scenario 4: Using nurse-endoscopists - For this scenario we assumed that nurse endoscopists can independently perform a procedure including polypectomy for lesions up to 1 cm in diameter and that one gastroenterologist than can supervise three nurse endoscopists. This meant that we accounted for one nurse endoscopist and one-third gastroenterologist per colonoscopy room. As a result, personnel costs for an NCol were €27.87 lower, and for one PCol €33.85 lower. The total average costs for one screening colonoscopy in this setting were €206.31 compared to €252.30 in the base-case.

Scenario 5: Extending the screening program into evening hours - Performing screening colonoscopies in the evening hours as well (3 extra hours) increased personnel costs (labor costs increase in the evening hours) but made better use of capacity. In total the costs would raise slightly with €0.11 per colonoscopy.

Scenario 6: *Screening colonoscopies performed with or without the use of sedation.* - Mean time spent at the recovery by participants without the use of sedatives was 15 minutes. In this scenario, only one bed was needed at the recovery room plus one bed for transport, and the nurse at the recovery room was only needed for 50% of time. Furthermore, costs for sedatives and pulse-oxymeters were eliminated. The total

average costs for one screening colonoscopy in this setting were €239.79 compared to €252.30 in the base-case.

Recovery room

A total of 1220/1426 (86%) participants received sedatives in combination with analgesics during colonoscopy. Analgesics alone were used in 58/1426 (4%) procedures; no medication was used in 133/1426 (9%). Butylscopolamine was used in 57% of colonoscopies. Costs of these medications are displayed in Table 3.

The mean time spent at the recovery was 59 minutes (range 13-119 minutes). Therefore, in both screening settings, two beds at the recovery room plus one bed for transport to and from the recovery room would be needed. However, assuming a worst case scenario, one extra bed with 8 m² extra recovery space would be needed in the dedicated screening setting, resulting in €0.22 extra costs per colonoscopy.

Table 3: personnel, non-personnel and overhead costs per stage per PCol and NCol in a dedicated screening setting (3510 colonoscopies per year).

Items	Costs per colonoscopy	Link table 2
Invitation		
Invitation letter	*€854 for printing 40,000 invitations = €0.02 per invitation*	Invitation procedure material
Information leaflet	*€987 for printing 3,300 leaflets = €0.30 per leaflet*	Invitation procedure material
Envelope	*€178 for1,500 envelopes = €0.12 per envelope*	Invitation procedure material
Postal charges	*80 grams, charge €0.88*	Invitation procedure material
Administrative worker	*Salary: €29,-/hr, 3 min/invitee = €1.53 per invitee*	Invitation procedure personnel
Other costs		
Overhead (42%)	*€2.14*	Invitation procedure material
Subtotal invitation	*€4.99*	
Reminder		
Reminder letter	*€854 for printing 40,000 reminders = €0.02 per reminder letter*	-
Envelope	*€178 for 1,500 envelopes = €0.12 per envelope*	-
Postal charges	*20 grams, charge €0.44*	-
Subtotal reminder	€0.58	
Pre-colonoscopy assessment by telephone		

Table 3: personnel, non-personnel and overhead costs per stage per PCol and NCol in a dedicated screening setting (3510 colonoscopies per year).

Confirmation letter	*€854 for printing 40,000 confirmations =€ 0.02 per confirmation letter*	Intake & scheduling appointment material
Envelope	*€178 for 1,500 envelopes = €0.12 per envelop*	Intake & scheduling appointment material
Postal charges	*20 grams, charge €0.44*	Intake & scheduling appointment material
Nurse	*Salary : €31,17/hr, 4 calls/hr =€ 7,84/call*	Intake personnel
Schedule appointment for colonoscopy		
Schedule appointment	*Salary administrative worker €29,-/hr, 20 calls/hr = 1,45/call*	Intake personnel
Confirmation letter	*€854 for printing 40,000 confirmations = €0.02 per confirmation letter*	Intake & scheduling appointment material
Information leaflet	*€854 for printing 40,000 pages = €0.02 per page*3 pages=€0.06*	Intake & scheduling appointment material
Large envelope bowelprep	*€0.20*	Intake & scheduling appointment material
Postal charges bowelprep	*120 grams: charge€2.64*	Intake & scheduling appointment material
Subtotal intake	*€12.79*	
Colonoscopy		
Reception		
Receptionist	*Salary : €29,-/hr, 60 participants/hr=€0.48*	Colonoscopy personnel
Nurse	PCol: (€2744 salary costs per month*12*1.08*1.37)/ 3276 = €14.87 NCol: (€2744 salary costs per month*12*1.08*1.37)/ 3978 = €12.25	Colonoscopy personnel
Gastroenterologist	PCol: (€135.50*8)/14 = €77.43 NCol: (€135.50*8)/17 = €63.76	Colonoscopy personnel
Nurse	PCol(€2744*12*1.08*1.37)/ 3276 = €14.87 NCol: €2744*12*1.08*1.37)/ 3978 = €12.25	Colonoscopy personnel
Subtotal colonoscopy personnel	PCol: €70.02	
Subtotal colonoscopy personnel	NCol: €88.74	
Materials		
Universal stretcher	Price: €2505, Life span: 10 yrs, ((2505/10)/3510)*3 = €0.21	Colonoscopy material
Mattress	Price: €208, Life span 6 yrs, ((208/6)/ 3510)*3 = €0.03	Colonoscopy material
Sheet	€0.63 per participant, 1 needed	Colonoscopy material
Datascope accutorr plus	Price: €7500, Life span 7 yrs: (7500/7)/ 3510 = €0.31	Colonoscopy material
Infusion needle	€2.97 per piece	Colonoscopy material

Table 3: personnel, non-personnel and overhead costs per stage per PCol and NCol in a dedicated screening setting (3510 colonoscopies per year).

Plaster	€0.37 per piece	Colonoscopy material
Alcohol	€0.09	Colonoscopy material
Gauzes	2 gauzes*€0.01= €0.02	Colonoscopy material
NaCl 0.9%	€0.62	Colonoscopy material
Syringe 10 cc	€0.04	Colonoscopy material
Bowel prep	*€16.21, Moviprep (Norgine bv, the Netherlands)*	Colonoscopy material
Suction bags	1 needed per 3 colonoscopies: €1.69*0.33= €0.56	Colonoscopy material
Plastic aprons	2 needed per colonoscopy: €0.02*2= €0.04	Colonoscopy material
Clothing	€32.84 Life span 250days((€32.84/250/24/60)*28)*3 needed per day = €0.008	Colonoscopy material
Washing clothing	(€2/day/15 colonoscopies per day)*2 uniforms= €0.26	Colonoscopy material
Gloves	€0.06*2 = €0.12	Colonoscopy material
Mat	3 needed per colonoscopy * €0.15 = €0.45	Colonoscopy material
Towel	€238.65 for 955 towels*1 needed = €0.25	Colonoscopy material
Washcloth	€44.0 for 550 washcloths*3 needed= €0.24	Colonoscopy material
Gauzes	€0.01*5 gauzes needed= €0.05	Colonoscopy material
Desufflation cannula	€0.31 for 5 cannulas = €0.06 per cannula	Colonoscopy material
Oxygen tube	1 used per 5 colonoscopies: €0.23*0.05 = €0.01	Colonoscopy material
Suction tube	€6.14 for 30 m, 3m/colonoscopy: €6.14*0.1 = €0.61	Colonoscopy material
Large syringe for rinsing	€0.30*70% of colonoscopies needed = €0.21	Colonoscopy material
Analgesics (Fentanyl 2ml)	€0.59*89.6% of colonoscopies used = €0.53	Colonoscopy material
Sedation (Midazolam 1 ml)	€0.89*85.5% of colonoscopies used = €0.76	Colonoscopy material
Butylscopolamine (20 mg)	€1.09*57% of colonoscopies used = €0.62	Colonoscopy material
Anexate (5 ml)	€20.27*5% of colonoscopies used = €1.01	Colonoscopy material
NaCL 0.9% (100ml)*	€0.62	Colonoscopy material
Lubricant	€1.48/tube for 5 colonoscopies: €1.48/5= €0.30	Colonoscopy material
Collecting tray polyps*	€175.77 for 25 trays, one/10 colonoscopies,(€175.77/25)*10% = €0.65	Colonoscopy material PCol
Suction needle for polyps*	€0.05 per piece	Colonoscopy material PCol
Roth net*	€59.76*5% of colonoscopies needed = €1.20	Colonoscopy material PCol
Formalin jar*	€22.99/50 jars*2.6 samples = €1.20	Colonoscopy material PCol

Table 3: personnel, non-personnel and overhead costs per stage per PCol and NCol in a dedicated screening setting (3510 colonoscopies per year).

Transport bag*	€0.03*1 = €0.03	Colonoscopy material PCol
Biopsy forceps*	€7.25*41% used for polypectomy = €2.96	Colonoscopy material PCol
Hot biopsy*	€20* 6% used for polypectomy = €1.18	Colonoscopy material PCol
Polypectomy snare*	€14* 51% used for polypectomy = €7.20	Colonoscopy material PCol
NaCl for lifting*	€0.62/100 ml, (€0.62/20% needed)*35% of polypectomies = €0.04	Colonoscopy material PCol
Adrenaline 0.5mg/ml*	€0.21/ml*7% of polypectomies needed = €0.01	Colonoscopy material PCol
Indian ink (5 ml)*	€0.36/5 ml*1.7% of PCol's needed = €0.01	Colonoscopy material PCol
Clip forceps (disposable)*	(€650/10)*2.7% of PCol's needed = €1.77	Colonoscopy material PCol
Subtotal colonoscopy material	PCol: €44.51	
Subtotal colonoscopy material	NCol: €28.21	
Investments		
ETD3	Price: €41000, Life span 10 yrs, (€41000/10)/3510 = €1.17	Colonoscopy investments
ETD3 maintenance	€2145/ year/ 3510 = €0.61	Colonoscopy investments
ETD3 standard	Price: 1280, Life span 10yrs, (€2180/10)/3510 = €0.04	Colonoscopy investments
Detergent ETD3	€706 for 32.4 L, (€706/32.4/1000)*30 ml needed per 2 colonoscopes = 0.33	Colonoscopy material
Colonoscope CF-H180AL	price: €33900, Life span 6yrs, ((€33900/6)/3510)*3 colonoscopes = €4.83	Colonoscopy investments
Contract CF-H180AL	(€2125/year/ 3510)*3 = €1.82	Colonoscopy investments
Maintenance CF-H180AL	(€172/contract/year/ 3510)*3 = €0.15	Colonoscopy investments
Video processor CV180	Price: €19988, Life span 10yrs, (€19988/10)/3510 = €0.57	Colonoscopy investments
Light processor CLV 180	Price: €12915, Life span 10yrs, (€12915/10)/ 3510 = €0.37	Colonoscopy investments
Scoop car WM-NP	Price: €3500, Life span 10yrs, (€3500/10)/ 3510 = €0.10	Colonoscopy investments
Monitor OEV261H	Price: €6300, Life span 7yrs, (€6300/7)/ 3510= €0.26	Colonoscopy investments

Table 3: personnel, non-personnel and overhead costs per stage per PCol and NCol in a dedicated screening setting (3510 colonoscopies per year).

Software Endobase	Price: €15000, Life span 5yrs, (€15000/5)/ 3510 = €0.85	Colonoscopy investments
Maintenance software	€2329/ year/ 3510 = €0.66	Colonoscopy investments
Irrigation pump OFP-2	Price: €2100, Life span 10yrs, (€2100/10)/ 3510 = €0.06	Colonoscopy investments
CO2 insufflator UCR	Price: € 6370, Life span 10yrs, (€6370/10)/ 3510 = €0.18	Colonoscopy investments
Pulse oxymeter	Price: €1300, Life span 10yrs, (€1300/10)/ 3510 = €0.05	Colonoscopy investments
Erbe VIO200D endocut*	Price:€11787,Life span 10yrs,(€11787/10)/ (3510*0.49 PCol's) = €0.69	Colonoscopy investments PCol
APC2*	Price: €7939, Life span 10yrs, (€7939/10)/ (3510*0.49 PCol's) = €0.46	Colonoscopy investments PCol
Footswitch Erbe*	Price: €797, Life span 10yrs, (€797/10)/ (3510*0.49 PCol's) = €0.05	Colonoscopy investments PCol
Argon probes disposable*	€926 for 10 probes/(3510*0.49 PCol's) = €0.05	Colonoscopy investments PCol
Regulator valve*	Price: €736, Life span 7yrs: (€736/7)/(3510*0.49 PCol's) = € 0.06	Colonoscopy investments PCol
Argon gas*	1000L/bottle, 2 L/(3510*0.49 PCol's) = (€52.02/1000)*2 = €0.10	Colonoscopy investments PCol
Neutral electrode*	€1 per electrode/49% PCol's = €0.49	Colonoscopy investments PCol
Cord for neutral electrode*	Price: €98, Life span 7yrs, (€98/7)/ (3510*0.49 PCol's) = €0.008	Colonoscopy investments PCol
Desktop Optiplex 780	Price: €586, Life span 5yrs, (€586/5)/3510 = €0.03	Colonoscopy investments PCol
Extra monitor 22 inches	Price: €149, Life span 5yrs, (€149/5)/3510 = €0.008	Colonoscopy investments PCol
Maintenance computer	€488/contract/year/3510 = €0.14	Colonoscopy investments PCol
Stickerprinter	Price: €386, Life span 5yrs, (€386/5)/3510 = €0.02	Colonoscopy investments PCol
Colonoscopy investments	*PCol: €14.10*	
Colonoscopy investments	*NCol: €12.19*	
Room	(65.40/ m²/year*24 m2)/ 3510 = €0.45	Recovery room
Subtotal recovery room	*€0.45*	
Overhead colonoscopy		

Table 3: personnel, non-personnel and overhead costs per stage per PCol and NCol in a dedicated screening setting (3510 colonoscopies per year).

Overhead (personnel and material costs) (42%)	Pcol: €166.71*0.42= €236.72 NCol: €129.05*0.42 = €54.20	Overhead colonoscopy
Subtotal overhead colonoscopy	PCol: €70.02	
Subtotal overhead colonoscopy	NCol: €54.20	
Pathological assessment*		
Laboratory assistant *	€34.42	PA personnel
Pathologist*	((€170471 salary costs per year/1540)/60)*3 min = €5.53	PA personnel
Material*	€5.27	PA non-personnel
Maintenance*	€13.89	PA non-personnel
Overhead (42%)*	€18.99	PA overhead
Subtotal PA	€78.10	
Final test results reported by general practitioner		
Letters test results	€854 for printing 40,000 pages = €0.02 per letter*2 =€0.04	Test results non-personnel
Envelopes	€178 for 1,500 envelopes =€ 0.12 per envelope*2=€0.24	Test results non-personnel
Postal charges	20 grams, charge €0.44*2=€0.88	Test results non-personnel
Telephone consultation*	€14.00 per consultation, 330/698 PCol's with adenomas: =14*(330/698) = €6.62	Test results personnel
Face-to-face consultation*	€28.00 per consultation, 9/698 PCol's with a carcinoma: = 28*(9/698) = €0.36	Test results personnel
Subtotal reporting test results	PCol: €8.14	
Subtotal reporting test results	NCol: €1.16	

DISCUSSION

Our aim with this analysis was to assess the actual unit costs of a primary screening colonoscopy based on data collected in a pilot CRC screening program, hypothesizing that these costs are lower than those of a clinical colonoscopy as expressed by hospital reimbursement rates. In a dedicated screening setting (our base-case), the costs per procedure were determined at €252.30. These are the costs for a weighed average (51%/49%) for positive and negative colonoscopies. In a non-dedicated setting ac-

counting for only 10 colonoscopies per day, this increased to €307.30, primarily due to higher personnel costs.

These unit costs are considerably lower than reimbursement rates used in the Netherlands; €393 for a colonoscopy with polypectomy and €303 for a colonoscopy without polypectomy resulting in a weighed average of €350 per colonoscopy. This difference shows how the use of clinical reimbursement rates as proxy for costs of colonoscopy impair the validity of cost-effectiveness analyses and result in underestimation of the cost-effectiveness of screening.

Our study is based on a large population-based RCT with a substantial number of screening colonoscopies allowing realistic cost estimates. Costs per invitation, pre-colonoscopy assessment and colonoscopy itself were based on the actual costs made. Time that was needed per intake, per colonoscopy and per pathological assessment was measured for all participants. We also took the logistics and different stages in screening fully into account. Given that costs for personnel, material and investments can differ per country, it is important that specific cost parameters can be varied in our calculations to calculate the true unit costs per screening colonoscopy for other situations, including the mix of positive and negative colonoscopies.

A disadvantage of our study is that we were not able to measure the personnel costs that were made by the screening organizations per invitation. Therefore, the average costs per invitation were calculated, dividing the overall personnel costs and overhead costs made by the screening organizations during the screening trial, by the overall number of invitations.

Time that was needed for the pathologists to assess one tissue sample was measured. Unfortunately, we were unable to measure assessment times for the lab assistants. Finally, we calculated the overhead costs by multiplying the personnel, material and maintenance costs by 42%.(56) Although a simplification, this is a standing approach in cost studies.

To our knowledge no previous empirical studies addressed the unit costs of population-based CRC screening using colonoscopy as the primary screening method, based on time measurements and costs made in a primary colonoscopy-screening pilot. Meanwhile, multiple cost-effectiveness analyses have been performed in the past. (38, 57, 58) Costs per colonoscopy were based on reimbursement rates. Internationally, these rates are usually lower than those in the Netherlands, and show a wide variation among situations and regions. For the United States, in a systematic review for the U.S. Preventive Services Task Force published in 2002, reimbursement rates for a colonoscopy without polypectomy varied between $285 and $1012 and with polypectomy between $434 and $1519. (59) In France reimbursement rates for a colonoscopy (with and without polypectomy) were €740 ($988.34) in 2010. These relatively high costs can partly be explained by the fact that in France over 90% of

colonoscopies are performed with anesthesiologist assistance. (60) Only in Germany, where colonoscopy is widely used as a primary CRC screening test, the reimbursement rates of insurance companies are lower. For a colonoscopy without histology the rate is €197, for a colonoscopy with histology but without polypectomy €209 and for a colonoscopy with polypectomy €245. (38)

An uncertainty in the costs for colonoscopy screening is possible discount prizes for materials and investments when colonoscopies are performed at large scale. However, as long as there is no nationwide population-based screening program for CRC in the Netherlands, we can only speculate on such discounts.

Screening colonoscopies performed by nurse endoscopists are another possibility to lower the costs considerably, as we investigated. This scenario might also provide a solution for the problem of insufficient endoscopic capacity for primary CRC screening. In the UK, nurse endoscopists contribute significantly to the CRC screening program. In 2005 more than 200 nurse endoscopists were practicing in the UK.(61) In the US in 2002, 6.1% of all screening sigmoidoscopies were performed by non-physician endoscopists. (62) There is less large-scale experience with colonoscopy in this respect. However, in 2007 in the Netherlands, a study was performed to determine the views of gastroenterologists and gastroenterology residents about the potential role of nurse endoscopists in gastrointestinal endoscopy. A majority of gastroenterologists had a positive attitude towards introduction of nurse endoscopists in colonoscopy screening, but not in diagnostic and therapeutic endoscopies. (63)

Colonoscopy screening without the use of sedatives is common practice in many countries. In Norway for example, most screening colonoscopies are performed without the use of intravenous sedatives. (64) On the other hand, in a Canadian study, more than 90% of gastroenterologists turned out to use sedatives during colonoscopy, and the majority of them preferred propofol sedation. (65) In our study, costs were €12.52 lower per colonoscopy when performed without sedatives (midazolam). When looking at colonoscopies with the use of propofol sedation, where an anesthesiologist is needed, savings will be even higher when reducing the use of sedation. (60)

When looking at the Dutch situation, offering 20% of the 55-75 aged population a colonoscopy every 10 years would imply approximately 99,000 screening colonoscopies per year. Not using sedatives for example, will result in lowering costs with €1.239,480 (99,000 * €12.52) per year. Assuming that nurse endoscopists can play a major role in colonoscopy screening, their introduction may further lower the average costs per colonoscopy with €43.07, which would represent €4.263,930 on a yearly basis in the Netherlands (99,000 * €43.07).

This analysis shows that the costs per colonoscopy in a dedicated screening setting in the Netherlands are considerably lower than the current reimbursement rate for colonoscopy in a clinical setting in symptomatic patients. Similar differences can

be expected in other countries. Since many economic evaluations have relied on reimbursement rates as a proxy for the unit costs of a screening colonoscopy, the actual costs per life-year saved through CRC screening with primary colonoscopy may be lower than estimated in these evaluations. Adjusting this to the lower screening costs will improve the cost-effectiveness of CRC screening with primary colonoscopy (decreasing the costs per life year gained), also relative to CRC screening strategies with other primary screening tests, e.g. FOBT. Increase in CRC screening practice in the general population will allow for further refinement of cost estimates for the various screening tests.

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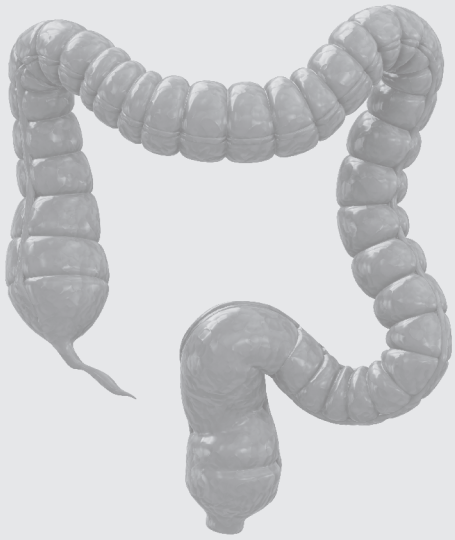
CHAPTER 5

Face-to-Face vs Telephone Pre-Colonoscopy Consultation in Colorectal Cancer Screening; a Randomized Trial



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ABSTRACT

Background: A pre-colonoscopy consultation in colorectal cancer (CRC) screening is necessary to assess a screenee's general health status and to explain benefits and risks of screening. The first option allows for personal attention, whereas a telephone consultation does not require traveling. We hypothesized that a telephone consultation would lead to higher response and participation in CRC screening compared with a face-to-face consultation.

Methods: 6,600 persons (50-75 yrs) were 1:1 randomized for primary colonoscopy screening with a pre-colonoscopy consultation either face-to-face or by telephone. In both arms, we counted the number of invitees who attended a pre-colonoscopy consultation (response) and the number of those who subsequently attended colonoscopy (participation), relative to the number invited for screening. A questionnaire regarding satisfaction with the consultation and expected burden of the colonoscopy (scored on five-point rating scales) was sent to invitees. Besides, a questionnaire to assess the perceived burden of colonoscopy was sent to participants, 14 days after the procedure.

Results: In all, 3,302 invitees were allocated to the telephone group and 3,298 to the face-to-face group, of which 794 (24%) attended a telephone consultation and 822 (25%) a face-to-face consultation (p=0.41). Subsequently, 674 (20%) participants in the telephone group and 752 (23%) in the face-to-face group attended colonoscopy (p=0.018). Invitees and responders in the telephone group expected the bowel preparation to be more painful than those in the face-to-face group while perceived burden scores for the full screening procedure were comparable. More subjects in the face-to-face group than in the telephone group were satisfied by the consultation in general: (99.8% versus 98.5%, p=0.014).

Conclusion: Using a telephone rather than a face-to-face consultation in a population-based CRC colonoscopy screening program leads to similar response rates but significantly lower colonoscopy participation.

INTRODUCTION

Screening programs for colorectal cancer (CRC) are being implemented in most Western countries. In 2009, 19 out of 27 European countries had established or were preparing a population-based or opportunistic CRC screening program. (66) Although screening for colorectal cancer is gaining acceptance throughout the world, a consensus on the preferred strategy is still lacking. Colonoscopy is a colorectal exam with a high accuracy to detect colorectal neoplasia and one of the recommended screening strategies by the US Taskforce. (6) Colonoscopy is, however, a burdensome procedure that requires complete colon lavage. For a primary screening test, it has a relatively high complication rate of 0.1% to 0.3%. (25, 26) When colonoscopy is used as a primary screening method, the risks and benefits of screening therefore have to be explained to participants before screening to enable informed decision making. Besides, information on a person's medical history and medication use should be obtained to anticipate on possible risks during colonoscopy. On one hand screenees need to be adequately informed on the risks and benefits of the procedure, and on the other hand the endoscopist and screening organization require adequate information on the health status of the individual screenee and the need for any specific precautions. Both aims can be achieved in a pre-colonoscopy consultation.

Most hospitals in the Netherlands invite patients at the outpatient clinic prior to colonoscopy. Although this is working well in daily clinical practice, it may overload the outpatient clinic when used in screening.

An alternative for a face-to-face consultation could be a telephone consultation. Travelling to and from the hospital with absence from home or work would no longer be necessary which could facilitate participation. On the other hand, bowel preparation may be less well explained during telephone conversations, which would lead to lower quality exams. Telephone conversations may provide less room for additional questions, leading to lower satisfaction levels and inferior participation rates. Furthermore, participants' expected burden of the colonoscopy might be influenced by the type of assessment.

The primary aim of this randomized trial was to compare the response rate and participation rate with pre-colonoscopy assessment by telephone to that of a face-to-face consultation at the outpatient clinic. Secondary outcomes were participants' satisfaction, expected and perceived burden, and quality of bowel preparation. Our *a priori* hypothesis was that more invitees would have a pre-colonoscopy assessment in the telephone group than in the face-to-face group, because these invitees could stay at home or at work during the consultation. We expected that a higher response rate in the telephone group would lead to a higher colonoscopy participation rate, because these invitees would have to come to the hospital only once. We also expected

participants in the face-to-face group to be more satisfied with the consultation and that the quality of bowel preparation would be higher in this group. We anticipated no difference between both groups regarding expected burden and perceived burden of the colonoscopy.

METHODS

Randomization and invitation

A group of 6,600 persons aged 50-75 years of the general Dutch population in the regions Amsterdam and Rotterdam was randomly allocated, prior to invitation, to either a face-to-face pre-colonoscopy consultation (n=3,298) or a telephone consultation (n=3,302) (Figure 1). Individuals were identified using the electronic databases of the regional municipal administration registration. Randomization was performed per household. The randomization was performed by TENALEA, using ALEA Randomization software (Version 2.2), based on a minimisation algorithm taking into account age (50-55, 55-60, 60-65, 65-70, 70-75), gender, and socio-economic status (very low, low, average, high, very high). At the time of the trial, the Netherlands did not have a CRC screening program.

All individuals were invited between June 2009 and July 2010 by the Regional Comprehensive Centers in Amsterdam and Rotterdam. They received a pre-announcement, followed by an invitation and an information leaflet, containing information on CRC in general, the advantages and disadvantages of screening, possible risks and follow up in case of a positive test result. If invitees failed to respond, they were sent a reminder letter four weeks later for the same assessment type as in the first invitation. (31) The overall design of the COCOS (COlonoscopy or COlonography for Screening) trial has been described in detail previously. (31) The primary outcomes of the COCOS trial (participation rate and diagnostic yield) were published recently. (67) Ethical approval was obtained from the Dutch Health Council (2009/03WBO, The Hague, The Netherlands). The trial was included in the Dutch trial register prior to its initiation: NTR1829 (http://www.trialregister.nl).

Pre-colonoscopy assessment

At two academic centers in the Netherlands, face-to-face and telephone pre-colonoscopy consultations were performed by clinical research staff. A formalized consultation was performed with standardized questions **(Table 1)** using a shared database in both hospitals. For both consultation types, 30 minutes were scheduled. During the consultation, possible screening exclusion criteria were discussed. Persons were excluded when they had had a full colonic exam (colonoscopy, double contrast

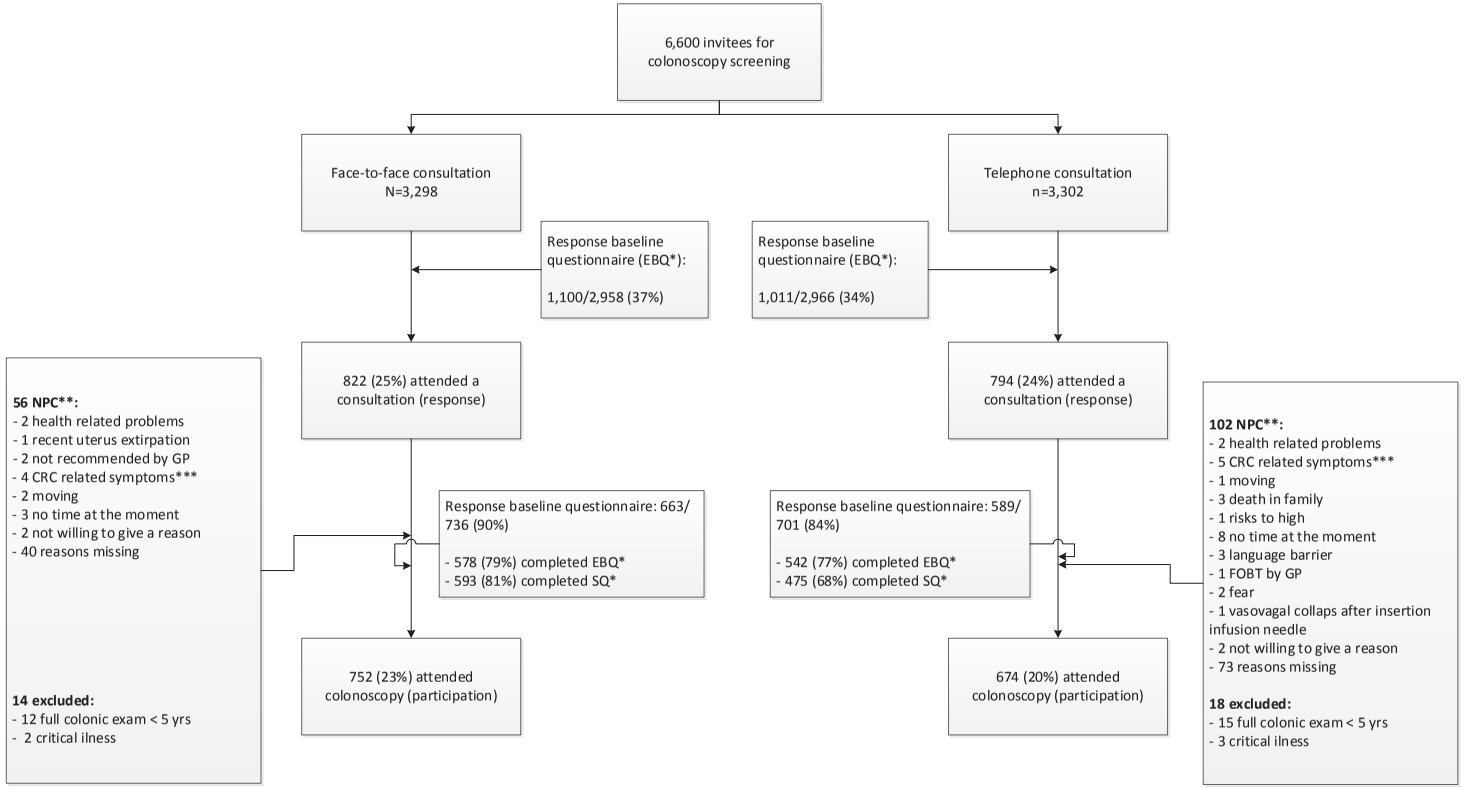

Figure 1: study flow: response, participation and questionnaire completion.
* Only a subsequent subset of 5,924 invitees received the baseline questionnaire. The participants belonged to this subset received the perceived burden questionnaire. The proportions of completed EBQ, SQ or PBQ are relative to this subset.
**Non-participant who attended the consultation.
***Subjects with CRC-related symptoms, referred by GP to gastroenterologist
EBQ: expected burden questions; SQ: satisfaction questions; PBQ: perceived burden questions

Table 1: Standardized questions asked during pre-colonoscopy consultation.

Standardized questions asked in both academic centers
Have you noticed rectal blood loss or changed bowel habits during the last three months?
Are you suffering from any chronic diseases, such as diabetes or asthma?
Are you suffering from any current diseases and if so, is specialized treatment necessary?
Have you ever been severely ill or admitted to the hospital? Have you ever had surgery?
Are you suffering from any chest pain, orthopnea, angina or exercise tolerance?
Are you taking medication and what are the corresponding dosages?
How tall are you and what is your weight? What is your nationality?
Do you use tobacco, alcohol or drugs? And if so, how many times a day?
Do you have first-degree relatives which have/had been diagnosed with CRC? Do you have first-degree relatives with hereditary diseases such as FAP or Lynch syndrome?

barium enema or CT colonography) in the previous 5 years or when they were in a surveillance program because of a personal history of CRC, colonic adenomas or inflammatory bowel disease. Persons with an end-stage disease and a life expectancy below 5 years were also excluded.

If additional information was needed on possible exclusion criteria or contra-indications for the screening procedure, the general practitioner or medical specialist was contacted for further information. In the telephone group, respondents were invited at the outpatient clinic if the research staff felt that the telephone consultation had been inadequate.

During the second part of the consultation, information was given regarding the colonoscopy itself. Duration, discomfort and possible complications, such as bleeding or perforation (0.1% to 0.3%) were discussed. The research staff explained about the possibility of using conscious sedation (midazolam) and/or analgesics (fentanyl) during the procedure.

Invitees received detailed information about the bowel preparation during the consultation. In addition, they were handed bowel preparation materials. In the telephone group, this was distributed by mail. At the end of the consultation, information was given on how test results would be reported and corresponding follow up measures. Informed consent was discussed during the assessment and subsequently, an informed consent form was sent by postal mail to potential participants together with an information leaflet for reference. Participants were asked to return the informed consent form by mail before the scheduled colonoscopy.

At the end of the consultation, an appointment was made for the actual colonoscopy. All individuals who agreed to participate were sent a confirmation of the appointment for colonoscopy.

Baseline questionnaire

The first 5,924 invitees received a validated baseline questionnaire by postal mail. Respondents to the first screening invitation received the questionnaire after the prior consultation, within four weeks before the scheduled colonoscopy. Invitees who had not responded to the initial invitation received the same baseline questionnaire four weeks after the initial invitation, together with the reminder. All individuals were asked to complete the questionnaire and to return it by mail in a pre-paid envelope.

The baseline questionnaire comprised items regarding satisfaction with the prior consultation (SQ) and expected burden (EBQ) of the colonoscopy **(Table 2).** Items on satisfaction were based on a previously validated questionnaire on satisfaction in eight university hospitals in The Netherlands. (68) Satisfaction was scored on a 4-point scale ranging from very satisfied to very unsatisfied. Expected burden was itemized into expected embarrassment, pain and burden of the bowel preparation and the colonoscopy itself and was previously validated. (15, 69, 70) The EBQ burden items such as embarrassment, pain and burden during the procedure were scored on five-point rating scales labelled as not embarrassing, painful or burdensome, to extremely embarrassing, painful or burdensome (1=not at all; 2=slightly; 3= somewhat; 4=rather; 5=extremely). The questionnaire also collected information on background characteristics such as educational and income levels. Completed baseline questionnaires were scanned and responses were automatically transferred to a database.

Table 2: Questions asked in baseline questionnaire regarding satisfaction and expected burden.

Satisfaction regarding the consultation
How satisfied are you with the personal attention?
How satisfied are you with the opportunity to ask questions?
How satisfied are you with the clarity of the information given during the assessment?
How satisfied are you with the assessment in general?
Expected burden of colonoscopy screening
How embarrassing do you expect the bowel preparation to be?
How painful do you expect the bowel preparation to be?
How burdensome do you expect the bowel preparation to be?
How embarrassing do you expect the colonoscopy to be?
How painful do you expect the colonoscopy to be?
How burdensome do you expect the colonoscopy to be?

Perceived burden questionnaire (PBQ)

A PBQ was sent to screening participants, two weeks after the colonoscopy **(Figure 1).** Participants received this questionnaire together with their final test results. Participants were asked to fill in the PBQ questionnaire directly after receiving it and to return by mail in a pre-paid envelope. If participants did not respond, they were

not reminded. This questionnaire had also been previously validated (15, 69-71). It comprised colonoscopy-related items as well as items on the full procedure (including bowel preparation, colonoscopy itself, post-procedure follow-up, and waiting for the test results. The perceived burden questions are listed in **Table 3.** All burden items were scored on a five-point rating scale ranging from not embarrassing, painful or burdensome to extremely embarrassing, painful or burdensome (1=not at all; 2=slightly; 3= somewhat; 4=rather; 5=extremely). Participants were also asked about their willingness to participate in a future screening round (1=absolutely not; 2=probably not; 3=probably; 4=certainly). Completed PBQs questionnaires were scanned and responses were automatically transferred to a database.

Table 3: Questions asked in perceived burden questionnaire

Bowel preparation
How embarrassing did you find the bowel preparation? How painful did you find the bowel preparation? How burdensome did you find the bowel preparation?
Insertion of the colonoscope
How embarrassing did you find insertion of the colonoscope? How painful did you find insertion of the colonoscope? How burdensome did you find insertion of the colonoscope?
The remainder of the examination
How embarrassing did you find the remainder of the colonoscopy? How painful did you find the remainder of the colonoscopy? How burdensome did you find the remainder of the colonoscopy?
Waiting for the test results
How burdensome did you find waiting for the test results?
The colonoscopy procedure overall
How embarrassing did you find the colonoscopy procedure overall? How painful did you find the colonoscopy procedure overall? How burdensome did you find the colonoscopy procedure overall?
Participation in a future screening round
Would you participate in a future colonoscopy screening round?

Colonoscopy

All colonoscopies were performed by experienced gastroenterologists (≥1000 colonoscopies) according to the standard quality recommendations of the American Society of Gastrointestinal Endoscopy. (52) Conscious sedation (midazolam) and analgesics (fentanyl) were administered intravenously at the discretion of the participant and the endoscopist. Withdrawal-time was at least 6 minutes. For bowel preparation, 2L of polyethylene electrolyte glycol solution (Moviprep; Norgine bv, Amsterdam, The Netherlands) together with 2L transparent fluid, and a low-fibre diet for two days were used. Bowel preparation was scored using the validated Ottawa bowel preparation

score (54) and classified as excellent (0-3), good (4-6), sufficient (7-10) or inadequate (11-14). In case of inadequate bowel preparation, the colonoscopy was interrupted and re-scheduled, unless the participant refused to undergo re-colonoscopy.

Data analysis

The analysis was based on the intention-to-screen principle. The primary outcome measures were the response rate, defined as the number of invitees attending the pre-colonoscopy consultation relative to the total number of invitees, and the participation rate, defined as the number of invitees who underwent a colonoscopy relative to the total number of invitees. Differences in response and participation rates between groups were evaluated using Chi-square test statistics. Results were not adjusted for clustering, as in most instances there were only one or two eligible subjects per household. Items on satisfaction of the consultation and expected and perceived burden of the colonoscopy were expressed as mean scores and compared using Mann-Whitney U test. Expected burden was compared for all invitees, responders (invitees who attended the consultation), and non-participants (responders who did not attend the colonoscopy). In the analysis of the expected burden and satisfaction scores for responders, questionnaires were excluded if completed before the consultation. All baseline questionnaires that had not been completed before the colonoscopy were excluded from the analysis. Quality of bowel preparation was expressed as percentages per category and compared using Chi-square statistics. The software program SPSS for Windows®, version 18, was used for all of the analyses.

Sample size

We expected an overall participation rate of 25% in colonoscopy screening. We anticipated a participation rate of 22.5% in the face-to-face group versus 27.5% in the telephone consultation group. Including 5,000 invitees in this trial would result in a power of 98% to reject the null hypothesis of no difference, using two degrees of freedom Chi-Square test with a significance level set at 0.05.

RESULTS

Response and participation

Figure 1 summarises the study flow. In the telephone group, 794 of the 3,302 invitees (24%) attended the pre-colonoscopy consultation versus 822 of the 3,298 invitees (25%) in the face-to-face group. This difference in response rate was not significant (p=0.41). One responder in the telephone group was invited at the outpatient clinic because of severe co-morbidity and was subsequently excluded from colonoscopy.

In total, 18 participants in the telephone group and 14 in the face-to-face group were excluded after the pre-colonoscopy assessment because they met one or more exclusion criteria. After the pre-colonoscopy consultation, 102 responders in the telephone group and 65 in the face-to-face group decided not to undergo a colonoscopy. The participation rate was significantly lower in the telephone group: 674 invitees (20%) had a screening colonoscopy after the telephone consultation versus 752 (23%) in the face-to-face group (p=0.018). Demographic characteristics of responders and participants are listed in **Table 4.**

Table 4: Demographic characteristics of responders and participants

	Pre-colonoscopy assessment (responders)		**Colonoscopy (participants)**	
Assessment type	Face-to-Face	Telephone	Face-to-Face	Telephone
Invitees (n)	3,298	3,302	3,298	3,302
Responders (n,%)	822 (25%)	794 (24%)	-	-
Participants (n, %)	-	-	752 (23%)	674 (20%)
Mean age (yr, SD)	61 (6.1)	60 (6.3)	61 (6.1)	60 (6.2)
Male (n,%)	419 (51%)	410 (52%)	387 (51%)	339 (50%)
SES* (mean, SD)	3.2 (1.4)	3.2 (1.4)	3.2 (1.4)	3.2 (1.4)

*Socio-economic status was categorized as very low, low, medium, high and very high (1-5)

Expected burden among all invitees

We had to exclude 27 questionnaires that were returned after the colonoscopy. Questions on expected burden were completed by 1,083 of 2,958 individuals (37%) invited for a face-to-face consultation and by 1,001 of 2,966 individuals (34%) invited for a telephone consultation.

Figure 2 summarises the expected burden scores of all invitees. Reluctance to undergo screening was comparable in both groups. The expected embarrassment and burden of the bowel preparation was scored comparable in both groups. A larger proportion of invitees allocated to the telephone consultation expected the bowel preparation to be somewhat painful: 26% versus 22%, with an overall mean score of 2.4 versus 2.3 (p=0.03). Mean scores for expected embarrassment, pain and burden of the colonoscopy itself were not statistically different between the two groups.

Expected burden among responders (invitees who attended the consultation)

Items on expected burden were completed by 578 of the 736 responders (79%) who attended a face-to-face consultation and by 524 of the 701 responders (75%) with a telephone consultation. Mean expected embarrassment and burden scores of the bowel preparation were similar for the two groups; the expected pain of the bowel

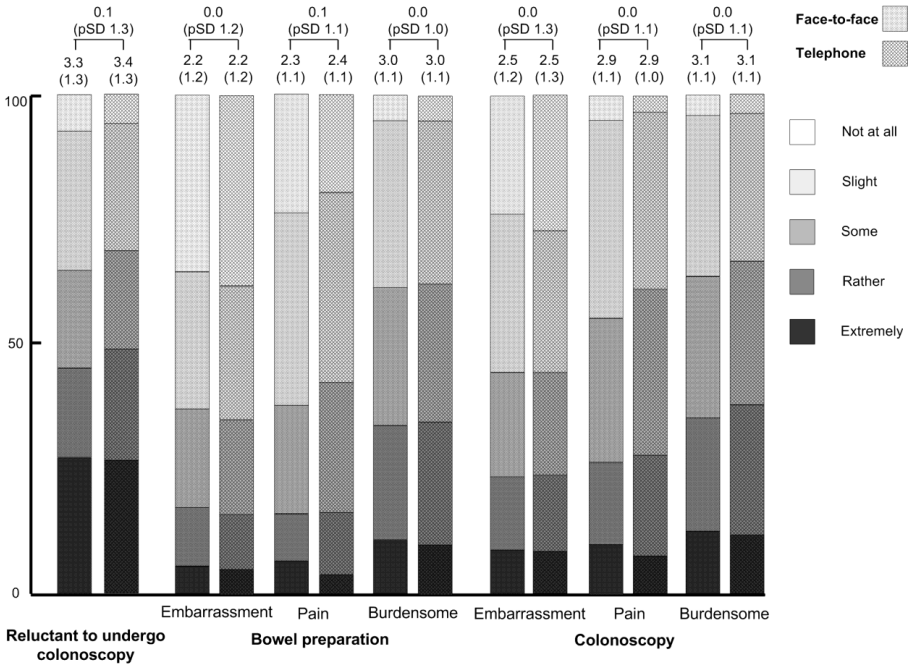

Figure 2: Reluctance to undergo colonoscopy and expected embarrasement, pain and burden of bowel prep and colonoscopy.
On top of the bars mean score, standard deviation (between parantheses), difference in mean scores and pooled standard deviation (pSD) are displayed. Expected pain of the bowel preparation differed significantly between the groups (p=0.03), all other items were not statistically different.

preparation was rated higher in the telephone group: 20% in the telephone group expected it to be rather painful versus 16% in the face to face group; overall mean scores were 2.1 versus 2.0 (p=0.03). Expected embarrassment, pain and burden of the colonoscopy itself were similar for both groups.

Expected burden in non-participants who did attend the consultation

In the telephone group 33 of the 102 non-participants (32%) completed the questions on expected burden versus 24 of the 56 (43%) in the face-to-face group. Scores on expected embarrassment, pain and burden of the bowel preparation and the colonoscopy itself did not significantly differ between the groups.

Satisfaction among responders

A total of 585 of the 736 responders (79%) in the face-to-face group completed the items on satisfaction after the consultation, versus 472 of the 701 responders (67%) in

the telephone group. **Table 5** summarizes the level of satisfaction during the consultation for both groups.

Almost all responders in the face-to-face group and in the telephone group indicated to be (very) satisfied with the assessment in general (99.8% versus 98.5%, p=0.014). Responders reported to be (very) satisfied with the personal attention from the research staff: 98.9% in the telephone group versus 100% in the face-to-face group (p=0.011). The clarity of the information given during the assessment was scored as (very) satisfying by 98.5% in the telephone group versus 99.5% in the face-to-face group (p=0.10). All responders (100%) in the face-to-face group expressed being satisfied with the possibility to ask questions versus 99.1% in the telephone group (p=0.023).

Table 5: Level of satisfaction

Satisfaction	Face-to-face n=585	Telephone n=472	P-value
The assessment in general	1.60 (SD 0.49)	1.69 (SD 0.50)	0.004
Possibility to ask questions	1.61 (SD 0.49)	1.70 (SD 0.49)	0.002
Personal attention	1.60 (SD 0.49)	1.72 (SD 0.48)	<0.001
Clarity of information	1.64 (SD 0.49)	1.75 (SD 0.48)	<0.001

Bowel preparation

Four colonoscopies in the telephone group and three in the face-to-face group had to be re-scheduled because of an inadequate bowel preparation. Mean Ottawa scores for the quality of the bowel preparation in participants were similar: 5.7 in the telephone group versus 5.6 in the face-to-face group (p=0.54) **(Table 6).**

Table 6: Quality of bowel preparation

Satisfaction	Face-to-face N=752	Telephone N=674	P-value
Excellent (0-3)*	225 (30%)	203 (30%)	0.92
Good (4-6)*	327 (43%)	283 (42%)	0.58
Sufficient (7-10)*	135 (18%)	118 (18%)	0.84
Inadequate (11-14)*	57 (8%)	62 (9%)	0.27
Missing	8 (1%)	8 (1%)	0.83

*Ottawa bowel preparation score

The perceived burden

In the telephone group, 574 (85%) colonoscopies were performed under conscious sedation in combination with analgesics compared to 647 (86%) colonoscopies in the

face-to-face group. (p=0.40). The PBQ was completed by 477 of 674 (71%) participants with a telephone consultation and 529 of 752 (70%) participants with a face-to-face consultation. Scores on perceived embarrassment, pain and burden of the full screening procedure were similar in both groups **(Figure 3)**. In participants, 95.5% in the telephone group and 96.2% in the face-to-face group would (probably) participate in a future screening round (p=0.58).

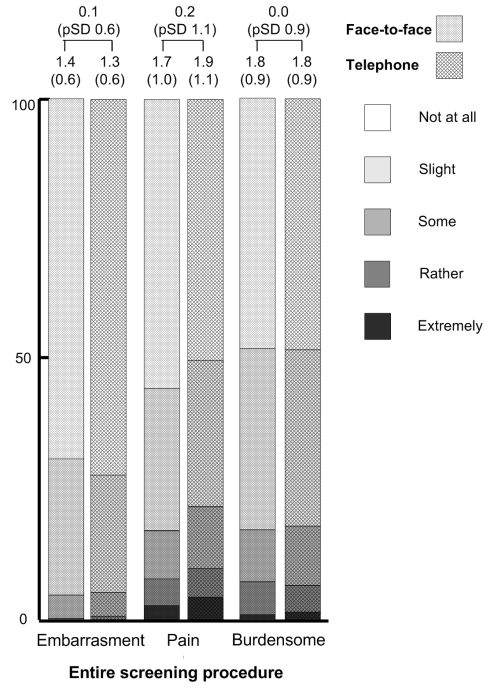

Figure 3: Perceived embarrassment, pain and burden of the entire screening procedure including bowel preparation, colonoscopy itself, waiting for the test results and abdominal complaints. On top of the bars mean score, standard deviation (between parentheses), difference in mean scores and pooled standard deviation (pSD) is displayed. None of the items were statistically different between the groups: pain (p=0.06), embarrassment (p=0.96) and burden (p=0.75).

DISCUSSION

We compared pre-colonoscopy consultation by telephone to face-to-face assessment in a population-based colorectal cancer screening program in average-risk subjects. The response rate was similar for telephone and face-to-face assessments, with about 25% of the invitees having the assessment. Colonoscopy participation on the other hand was significantly higher among individuals in the face-to face group. Satisfac-

tion was marginally but significantly lower and expected burden scores higher after telephone assessment.

Our study has several strengths. All invitees in this randomized controlled trial were screening naïve subjects and were randomly selected prior to the invitation to one of the two consultation types. Invitees received an invitation for only one of the two consultation types in combination with an identically designed detailed information leaflet. In this way, information supply and decision making was kept as simple and clear as possible. Information provided during the consultation was kept similar; a standardized questionnaire was used to keep the two assessment types comparable. In each center the same research staff performed both types of assessments, minimizing bias in the comparison. Nevertheless, differences may have occurred in the information exchanged with invitees. At the outpatient clinic, information supply can be simplified and made clearer using visual aids, for example.

In our study, 20% of the invitees in the telephone group participated in screening and 23% in the face-to-face group. This compares well with the attendance rates in other colonoscopy screening programs. The participation rate in colonoscopy population screening in Australia was 16%. (34) Two Italian randomized controlled trials, in which invitees were selected by general practitioners, reported primary colonoscopy participation rates of 10% and 27%. (32, 72) The annual participation rates for the age group 55 to 69 years in the opportunistic colonoscopy screening program in Germany are 3% for men and 4% for women (33).

To our knowledge only one previous, non-randomized study compared a face-to-face pre-colonoscopy assessment to a telephone assessment in CRC screening using gFOBT as the primary screening method.(73) This retrospective study, performed in Scotland, compared participation, satisfaction of the participant, and quality of bowel preparation in 316 gFOBT positive participants in the first year of screening (with a face-to-face consultation) with 388 gFOBT positive participants in the second year of screening (with a choice for face-to-face or telephone consultation). Overall, colonoscopy attendance was significantly higher in the second year: 99% versus 85%. These results our difficult to compare to ours, because of the non-randomized nature of the study and the optional choice for a face-to-face interview in the second year. Both in the Scottish study and in our study, quality of bowel preparation did not differ between the two groups.

Prior to colonoscopy, accurate information on bowel preparation must be provided to perform a high quality exam. Inadequate bowel preparation can result in missed lesions, cancelled procedures, increased procedural time, and a potential increase in complication rates. Adherence to instructions for preparation can be achieved by an accurate explanation prior to colonoscopy. Characteristics like age, gender, weight, and co-morbidity must be obtained before colonoscopy, because these may influence

the quality of bowel preparation. (74) Here also, in screening participants we found no significant differences between both groups. This indicates that a telephone interview can be an adequate mode for preparing participants for colonoscopy.

In our study we found significant differences in satisfaction between groups. It is conceivable that when participants feel satisfied with the personal attention and the opportunity to ask questions they will be more compliant with screening. One may assume that a high level of satisfaction strengthens continuity of the participant-physician relationship. (75, 76) Several previous studies have evaluated satisfaction regarding the colonoscopy (77-79). In concordance with our results, usually very high satisfaction rates are found. (80)

Expected burden may also influence participation in CRC screening. If invitees expect the colonoscopy to be highly burdensome, they can decide, before or after the pre-colonoscopy assessment, not to undergo colonoscopy. (79, 81) Expected burden can be influenced by the way the information is provided during the pre-colonoscopy assessment. In our study, significantly more invitees and responders in the telephone group expected the bowel preparation to be painful than in the face-to-face group. Not only expected burden but also perceived burden of colonoscopy influences the participation rate in future screening rounds. In our study, perceived burden was comparable between both groups as well as the willingness to participate in a future screening round (96%). This suggests that the mode of pre-colonoscopy assessment does not affect the experience of actual screening participants.

Actual differences in satisfaction and expected burden scores between both groups were small, which makes the clinical relevance arguable. In a review published in 2003, the minimally important difference (MID) for health-related quality of life instruments was computed. In this review, the authors concluded that, to indicate clinical relevance, a difference of at least half a standard deviation is needed. (82) However, colorectal cancer screening by definition has to deal with large populations, and the impact of screening fully relies on consistent participation during repeated screening rounds. As such, small differences become relevant.

It is possible that other factors, besides expected burden and satisfaction with the assessment, caused invitees in the telephone group to refrain more often from actual participation. Unfortunately, a considerable proportion of responders who did not attend colonoscopy failed to report the reason for not participating. Maybe the way in which the contact is initiated affects the developing physician-patient relationship. We know from other studies that this relationship can be influenced by the way participants are approached. (83, 84) Non-verbal communication between a doctor and a patient affects patient's satisfaction. Behavior such as sitting close to the patient and leaning forward have been associated with higher patient satisfaction. (85, 86) A Dutch study reported on endpoints in medical communication to improve physician

– patient communication. (87) The authors suggested that one of the ways to check if a good physician-patient relationship is being established is to have eye-contact with the patient, something which is obviously not possible during a telephone conversation. Having eye-contact also enables the physician to check whether information given during the assessment is understood.

Although, response rates in both groups were similar, the telephone group had a higher post-consultation drop-out rate, or in other words a lower post-consultation uptake of colonoscopy, which is of key importance for the impact of colorectal cancer screening. The uptake rate of colonoscopy using a telephone consultation needs to be improved. Therefore, further research should focus on how to raise colonoscopy participation rate after a telephone consultation. Maybe an interactive conversation using a computer, or information about the screening colonoscopy on video might increase commitment. Besides, information supply could be done using internet or email.

There may be alternatives to the face-to-face assessment as done in this study to evaluate and inform potential screening participants. One example is the additional use of a pre-assessment questionnaire. Future research should investigate the safety and preference of additional measures for improving pre-colonoscopy assessment in colonoscopy screening.

In summary, we found that a similar number of invitees responded to an invitation for a telephone consultation and to an invitation for a face-face consultation in a population-based colorectal cancer screening program using colonoscopy as the primary screening method. The number of invitees who decided not to participate was significantly higher after the telephone assessment, while satisfaction was lower and expected burden higher. We therefore do not recommend switching to telephone consultation in primary colonoscopy screening programs for colorectal cancer.

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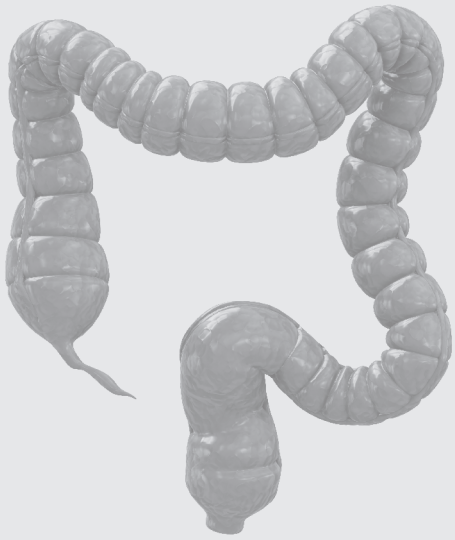
CHAPTER 6

Immunochemical Fecal Occult Blood Testing is Equally Sensitive for Proximal and Distal Advanced Neoplasia



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ABSTRACT

Objective: Fecal immunochemical testing (FIT) is increasingly used for colorectal cancer (CRC) screening. We aimed to estimate its diagnostic accuracy in invitational population screening measured against colonoscopy.

Methods: Participants (50-75 years) in an invitational primary colonoscopy screening program were asked to complete one sample FIT before colonoscopy. We estimated FIT sensitivity, specificity and predictive values in detecting CRC and advanced neoplasia (carcinomas and advanced adenomas) for cut-off levels of 50 (FIT50), 75 (FIT75) and 100 (FIT100) ng Hb/ml, corresponding with, respectively, 10, 15 and 20 microgram hemoglobin per gram feces.

Results: A total of 1,256 participants underwent a FIT and screening colonoscopy. Advanced neoplasia was detected by colonoscopy in 119 (9%); 8 (0.6%) of them had CRC. At FIT50, 121 (10%) had a positive test result; 45 (37%) had advanced neoplasia and 7 (6%) had CRC. A total of 74 of 1,135 FIT50 negatives (7%) had advanced neoplasia including 1 (0.1%) CRC. FIT50 had a sensitivity of 38% (95% CI: 29-47) for advanced neoplasia and 88% (95% CI: 37-99) for CRC at a specificity of 93% (95% CI: 92-95) and 91% (95% CI: 89-92), respectively. The positive and negative predictive values for FIT50 were 6% (95% CI: 3-12) and almost 100% (95% CI: 99-100) for CRC, and 37% (95% CI: 29-46) and 93% (95% CI: 92-95) for advanced neoplasia. The sensitivity and specificity of FIT75 for advanced neoplasia were 33% (95% CI: 25-42) and 96% (95% CI: 94-97). At FIT100, 71 screenees (6%) had a positive test result. The sensitivity and specificity of FIT100 were for advanced neoplasia 31% (95% CI: 23-40) and 97% (95% CI: 96-98), and for CRC 75% (95% CI: 36-96) and 95% (95% CI: 93-96). The area under curve for detecting advanced neoplasia was 0.70 (95% CI: 0.64-0.76). FIT had a similar sensitivity for proximal and distal advanced neoplasia at cutoffs of 50 (38% versus 37%; p=0.99), 75 (33% versus 31%; p=0.85) and 100 (33% versus 29%; p=0.68) ng Hb/ml.

Discussion: Nine out of ten screening participants with colorectal cancer and four out of ten with advanced neoplasia will be detected using one single FIT at low cutoff. Sensitivity in detecting proximal and distal advanced neoplasia is comparable.

STUDY HIGHLIGHTS

What is current knowledge?

- Population screening for colorectal cancer (CRC) with guaiac FOBT leads to a reduction in CRC-related mortality.

- Fecal Immunochemical Testing (FIT) is preferred over guaiac-FOBT because of the higher participation and detection rate at equal specificity in population screening.
- Solid data evaluating FIT (OC-Sensor) against colonoscopy are scarce.

What is new here?

- Within an invitational colonoscopy screening program, nine out of ten screening participants with CRC and four out of ten screening participants with advanced neoplasia will be detected using one single FIT.
- Sensitivity of FIT for the detection of proximal and distal neoplasia is equal.

INTRODUCTION

Colorectal cancer (CRC) is a major health problem worldwide.(1) The prognosis of patients is largely determined by the clinical and pathological stage at the time of diagnosis.(2) Population screening for CRC has shown to be beneficial which is explained by the high prevalence of disease, the slow progression from adenoma to clinically invasive cancer and its recognizable precursor lesions.(3-5)

All U.S. CRC screening guidelines include Fecal Immunochemical Testing (FIT) as one of the recommended screening tests.(6;7) The noninvasive character of FIT benefits adherence, although participation rates widely vary between countries.(8-11) Guaiac-FOBT (gFOBT) has shown to decrease CRC-related mortality by 16% and in a very cost-effective way.(4;12) FIT gains preference over gFOBT because of the higher acceptance and detection rates at equal specificity.(10;11) Furthermore, the quantitative measurement of hemoglobin (Hb) allows adaptation of the cutoff level for referral for colonoscopy to optimize cost-effectiveness or to account for the available colonoscopy capacity in a certain region.(13;14) Although FIT screening is implemented worldwide, solid data evaluating FIT against colonoscopy as the reference standard are scarce as most studies to date have only performed colonoscopy in subjects with a positive FIT, but not in those with a negative FIT.

In addition, the debate regarding miss-rates of right-sided neoplasia in CRC screening programs is also relevant for FIT. FIT aims to detect blood in stool but hemoglobin from proximal neoplasia may degrade on passage to the anus which could affect the accuracy of FIT. Second, a positive FIT-result is followed by a colonoscopy. Undetected right-sided neoplasia by colonoscopy will result in a lower sensitivity for detecting colorectal neoplasia in FIT screening.

We aimed to estimate the sensitivity, specificity, positive and negative predictive values of FIT in screening naïve participants within a population-based invitational

primary colonoscopy screening trial, using colonoscopy as the reference test. In addition, we aimed to evaluate FIT sensitivity in detecting right-sided and left-sided advanced neoplasia.

METHODS

Study population

Between June 2009 and July 2010, a total of 6,600 asymptomatic individuals of the Amsterdam and Rotterdam region were randomly selected from the regional municipal administration registrations and invited for colonoscopy screening. The protocol of this population-based screening pilot (COCOS-trial) has been described in detail previously.(15) The results on participation and diagnostic yield of this trial were published recently.(16) The trial was registered in the Dutch Trial Register: NTR1829 (http://www.trialregister.nl). At the time of the trial, the Netherlands did not have a population-based CRC screening program. Invitees who had had a full colonic examination in the previous 5 years (complete colonoscopy, CT colonography and/or double contrast barium enema) were excluded from the screening program. Invitees planned for surveillance colonoscopy (personal history of CRC, colonic adenomas or inflammatory bowel disease) and individuals with an end-stage disease and a life-expectancy of less than 5 years were also excluded. Ethical approval was obtained from the Dutch National Health Council (2009/03WBO, The Hague, The Netherlands).

FIT

Screening participants allocated to the colonoscopy arm of the COCOS-trial and willing to underg.o colonoscopy were informed about this study and invited to complete one sample FIT (OC-Sensor, Eiken Chemical Co., LTD., Japan) prior to their screening colonoscopy. Participants were verbally instructed at the screening center or at home. Screenees who agreed to participate gave written informed consent.

Consenting screening participants were provided with a study kit. The study kit contained a plastic collection container, a holder to position the container for collection, a FIT, a plastic bag to seal the FIT and written instructions on how to perform the FIT. No dietary or medication restrictions were advised. After emptying the bladder, but before having a bowel movement, participants were instructed to place the collection container into the holder, to avoid contamination with water or urine. After collection of one bowel movement they were instructed to sweep the tip of the probe several times through the feces and to insert the probe in the collection tube. The collection tube contained 2.0 ml of buffer designed to minimize the degradation of

hemoglobin. Afterwards, the FIT was sealed in a plastic bag and temporary stored in a sealed envelope at room temperature.

Participants were instructed to perform the FIT at home, within 48 hours before the colonoscopy, but before starting the bowel preparation, and were asked to bring the FIT to the screening center. Another option for FIT collection was to call the screening center immediately after performing the FIT, so that the research staff could collect the FIT within 48 hours at home.

Afterwards, the FIT was directly stored in a -20ºC freezer at the laboratory. The samples were automatically processed and analyzed within 6 weeks after storage to avoid degradation of hemoglobin at the Laboratory Clinical Chemistry of the Academic Medical Center in Amsterdam, which is certified according to CCKL (ISO 9001). FIT was only analyzed in the presence of written informed consent for both colonoscopy and FIT. FIT yielded a quantitative hemoglobin (Hb) concentration defined per milliliter test kit buffer (ng/ml). For the test used, an Hb concentration of 50, 75 and 100 ng/ml in the test buffer corresponds to, respectively, 10, 15 and 20 µg Hb/g faeces.

Colonoscopy

All colonoscopies were performed according to the standard quality indicators defined by the Society of Gastrointestinal Endoscopy and recorded on DVD (17). Research staff attended all colonoscopies and prospectively recorded colonoscopy quality indicators and data on polyp detection. Participants received a standard bowel preparation including a low-fiber diet and oral intake of 2 L of hypertonic polyethylene glycol solution (Moviprep, Norgine bv, Amsterdam, The Netherlands) and of 2 L of transparent fluid. Colonoscopies were performed under conscious sedation using intravenous midazolam (Dormicum, Actavis, Baarn, The Netherlands) and fentanyl (Bipharma, Weesp, The Netherlands) if desired. Endoscopists were highly experienced and had performed at least 1000 colonoscopies before the start of the study. Endoscopists were blinded from the result of FIT.

Bowel preparation was scored using the validated Ottawa bowel preparation score ranging from 0 (an excellent bowel preparation in all three colonic segments) to 14 (a very poor bowel preparation).(18) In case of insufficient bowel preparation, as much fluid and fecal residue as possible was suctioned out during intubation to inspect the colon as properly as possible. Subsequently, colonoscopy was rescheduled if considered necessary.

Cecal intubation was confirmed by documentation of cecal landmarks (cecal valve and appendix orifice or intubation of terminal ileum). During withdrawal of the colonoscope the colonic mucosa was carefully inspected. Minimal withdrawal time was at least six minutes. Size, morphology, localization and macroscopic aspect of all detected polyps were noted on a case record form. The size of all polyps was mea-

sured during endoscopy using a biopsy forceps with a 7 mm span. Localization was considered proximal when proximal to the splenic flexure. Morphology was assessed as sessile, pedunculated, flat or depressed. All detected polyps were directly removed and obtained for histological assessment. If immediate endoscopic treatment was not possible, biopsies were obtained to provide a histopathological diagnosis.

Histology

Removed lesions were assessed by one of two expert gastro-intestinal pathologists, one in each center. Lesions were classified as non-neoplastic, serrated polyp (hyperplastic, traditional serrated adenoma or sessile serrated lesion), adenoma (tubular, tubulovillous or villous) or carcinoma.(19) Dysplasia was defined as either low-grade or high-grade. Advanced adenoma was defined as an adenoma $\geq$ 10 mm, an adenoma with villous histology ($\geq$25% villous), and/or an adenoma with high grade dysplasia. Advanced neoplasia included an advanced adenoma and/or carcinoma. All advanced neoplasia and a random selection of 10% of all other neoplasia was re-examined by the pathologist of the other center. In case of inconsistency, the slides were reviewed together to provide a definitive diagnosis.

Outcome measures and statistical analysis

All screening participants who completed a FIT and underwent a screening colonoscopy were included in the analysis. A participant was considered screen positive if one or more advanced neoplasia were detected at the specified cut-off level. In addition, sensitivity, specificity and likelihood ratios were also estimated for detecting at least one advanced adenoma and a colorectal carcinoma. Sensitivity, specificity and likelihood ratios were estimated for FIT cut-off levels 50, 75 and 100 ng/mL. The number needed to screen (NNS) describes the number of FITs needed to detect one advanced adenoma, CRC or advanced neoplasia. Overall performance of FIT was evaluated by estimating the corresponding area under the Receiver Operating Characteristic (ROC) curve. The ROC curve was represented by plotting the sensitivity versus 1 minus specificity.

Sensitivity in detecting proximal and distal advanced neoplasia was estimated in participants with isolated proximal and isolated distal advanced neoplasia (i.e. participants with advanced neoplasia in both proximal and distal colon were excluded) and compared using Chi square statistic. Results were reported according to the standards for reporting diagnostic accuracy (STARD).(20)

RESULTS

Figure 1 shows the study flow. Of the 6,600 people invited for a screening colonoscopy, 1,616 (24%) responded and received a prior consultation. Thirty-four invitees had to be excluded from colonoscopy screening because of a complete bowel examination in the previous 5 years (n=26), planned surveillance colonoscopy (n=4), or end-stage disease (n=4). Another 156 invitees did not undergo colonoscopy after the prior consultation, leaving 1,426 participants who underwent a screening colonoscopy. Of these, 1,256 (88%) colonoscopy participants had consented to be included in this study and to perform a FIT. Population demographics are summarized in **Table 1**.

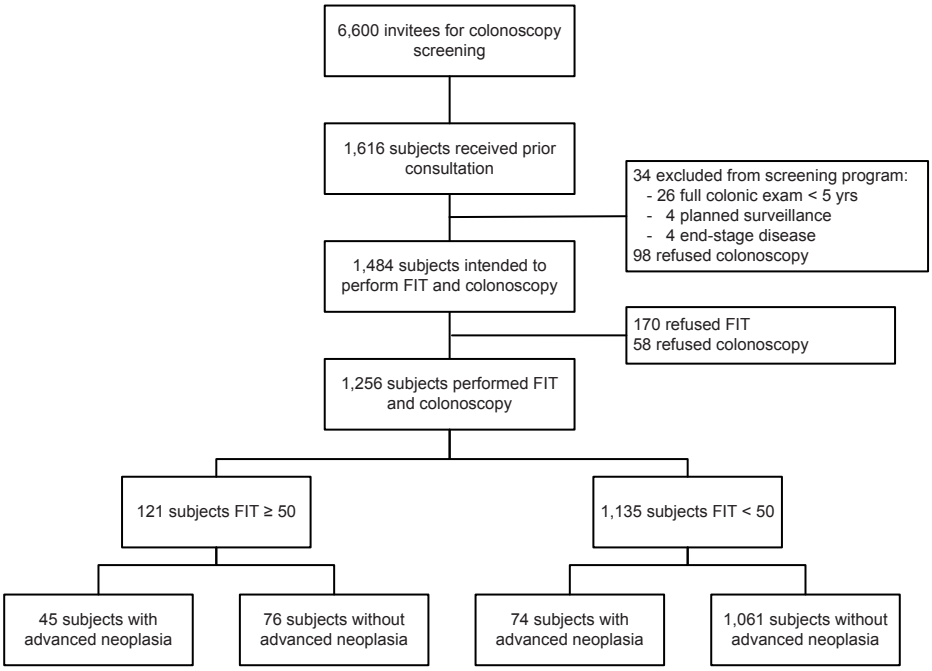

Figure 1: Study Flow.
Flow-chart according to STARD. Participant and endoscopist were blinded from the FIT-result. FIT was not analyzed in absence of written informed consent for colonoscopy or FIT.

Colonoscopy results

Of all FIT participants, the cecum was reached in 1,239 (99%). Inspection time during withdrawal was more than 6 minutes in almost all colonoscopies (99.8%). Median Ottawa bowel preparation score was 5 (IQR 3 to 8). At discretion of the endoscopist, 21 colonoscopies were considered incomplete (1.6%). Seven participants had persistent insufficient bowel preparation after additional endoscopic cleaning. It was

Table 1: Population demographics

Age (years, median, IQR)	60 (55-65)
Male (n, %)	726 (51%)
Social economic status	
– *Very low (n,%)*	171 (14%)
– *Low (n,%)*	260 (21%)
– *Average (n,%)*	259 (21%)
– *High (n,%)*	250 (20%)
– *Very high (n,%)*	303 (24%)
Ethnicity*	
– *Caucasian (n,%)*	998 (96%)
– *Other (n,%)*	37 (4%)
Education*	
– *Elementary (n,%)*	42 (4%)
– *Secondary (n,%)*	711 (68%)
– *Tertiairy and postgraduate (n,%)*	273 (26%)
Family history CRC	
– *One first-degree relative < 50 years (n, %)*	20 (2%)
– *One first-degree relative ≥ 50 years (n, %)*	158 (13%)
– *Two first-degree relatives ≥ 50 years (n, %)*	15 (1%)

*As not all participants completed the questions on their ethnicity and education, the percentages mentioned for these items are based on the participants who answered those questions.

not possible to intubate the cecum in 14 participants because of bowel anatomy or experienced pain.

No polyps were detected in 633 participants (50%). A total of 51 participants (4%) were detected with only non-neoplastic lesions, 192 (15%) with only serrated polyps and 261 (21%) with only non-advanced adenomas. Overall, adenomas (non-advanced and advanced altogether) were detected in 377 participants (30%) and advanced adenomas in 113 (9%). Eight participants (0.6%) had a carcinoma. Of the latter group, six were diagnosed with Dukes' stage A, 1 with Dukes' stage B and 1 with Dukes' stage C. Advanced neoplasia were detected in 119 participants (9%), i.e. two participants with CRC in addition had one or more advanced adenomas.

FIT results

Of 1,256 participants, 121 (10%) had a positive FIT result at a cut-off level of 50 ng/mL (FIT50), while 88 (7%) and 71 (6%) had a positive FIT result at a cut-off level of 75 ng/mL (FIT75) and 100 ng/mL (FIT100), respectively. In the FIT50 group of screen positives, advanced adenomas were detected in 40 participants, CRC in 7 participants, and advanced neoplasia in 45 participants. In the 1,135 FIT50 negatives, 73 (6%) par-

ticipants had advanced adenomas detected at colonoscopy, 1 (0.1%) CRC (Dukes A; 7 mm located in rectum) and 74 (7%) advanced neoplasia. In this population, raising the cut-off from 50 to 75 ng/mL would have missed a Dukes A carcinoma of 10 mm located in the rectum, an advanced adenoma of 20 mm in the ascending colon and four advanced adenomas of respectively 10, 12, 20 and 50 mm located in the rectum. Raising the cut-off from 75 ng/mL to 100 ng/mL would have missed a further two advanced adenomas of 7 and 10 mm in size located in the sigmoid and descending colon (Appendix)

FIT sensitivity, specificity, PPV, NPV and NNS

The accuracy of FIT in detecting advanced adenomas, CRC, and advanced neoplasia at the respective cut-off levels is summarized in **Table 2**. At a 50 ng/mL positivity cutoff, FIT had a sensitivity of 38% (95% CI: 29 to 47) for advanced neoplasia at a specificity of 93% (95% CI: 92 to 95). Using a 75 ng/mL cutoff, sensitivity and specificity in detecting advanced neoplasia were estimated at 33% (95% CI: 25 to 42) and 96% (95% CI: 94 to 97) respectively. Corresponding numbers for the 100 ng/mL threshold were 31% (95% CI: 23 to 40) and 97% (95% CI: 96 to 98).

Table 2: Accuracy of FIT at different cut-off levels for different disease outcomes

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)
FIT ≥ 50						
AA	35 (27-45)	93 (91-94)	33 (25-42)	94 (92-95)	5.0 (3.6-6.9)	0.70 (0.61-0.80)
CRC	88 (47-99)	91 (89-92)	6 (3-12)	100 (99-100)	9.6 (7.0-13.1)	0.14 (0.02-0.86)
AN	38 (29-47)	93 (92-95)	37 (29-46)	93 (92-95)	5.7 (4.1-7.8)	0.67 (0.58-0.77)
FIT ≥ 75						
AA	31 (23-40)	95 (94-96)	40 (30-51)	93 (92-95)	6.7 (4.6-9.8)	0.72 (0.64-0.82)
CRC	75 (36-96)	93 (92-95)	7 (3-15)	100 (99-100)	11.4 (7.3-17.4)	0.27 (0.08-0.89)
AN	33 (25-42)	96 (94-97)	44 (34-55)	93 (92-95)	7.6 (5.2-11.1)	0.70 (0.62-0.80)
FIT ≥ 100						
AA	29 (21-39)	97 (95-98)	46 (35-59)	93 (92-95)	8.8 (5.7-13.4)	0.73 (0.65-0.82)
CRC	75 (36-96)	95 (93-96)	8 (3-18)	100 (99-100)	14.4 (9.0-22.9)	0.26 (0.08-0.88)
AN	31 (23-40)	97 (96-98)	52 (40-64)	93 (91-94)	10.4 (6.8-15.9)	0.71 (0.63-0.80)

AA = advanced adenoma; AN = advanced neoplasia; CI = confidence interval; CRC = colorectal carcinoma; FIT = fecal immunochemical testing; PPV = positive predictive value; NPV = negative predictive value; LR+ = likelihoodratio positive; LR- = likelihoodratio negative

At the 50 ng/mL cut-off level, the positive predictive value for advanced adenoma, CRC, and advanced neoplasia was 33%, 6% and 37%, respectively. Corresponding negative predictive values at this threshold were 94%, almost 100% and 93%, respectively. **Figure 2** shows the ROC-curve of FIT for detecting advanced neoplasia. The area-under-curve (AUC) for detecting advanced neoplasia was 0.70 (95% CI: 0.64 to 0.76). Exclusion of participants with an incomplete colonoscopy provided similar results (data not shown).

At a cut-off level of 50 ng/mL, the number needed to screen to detect one participant with advanced adenoma, CRC and advanced neoplasia was 31, 179 and 28, respectively. Corresponding numbers at 75 ng/mL were 36, 209, and 32 versus 38, 209 and 34 at 100 ng/mL.

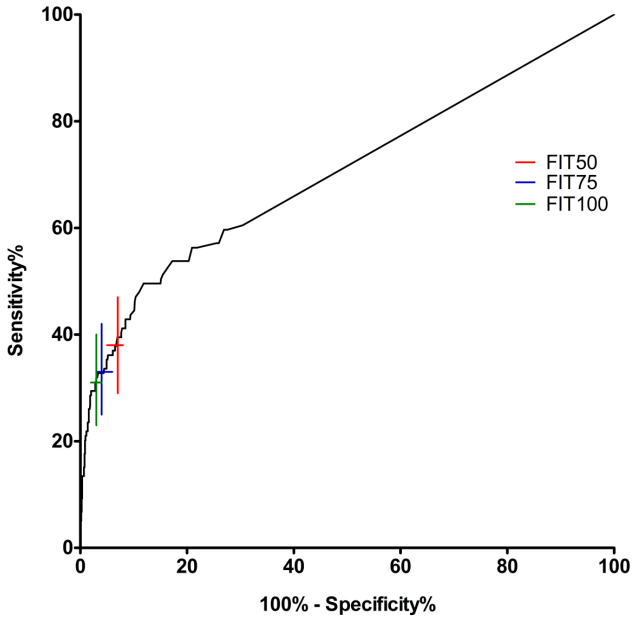

Figure 2: ROC-curve of FIT for detecting advanced neoplasia.
ROC-curve at different cut-off levels including confidence intervals for sensitivity and specificity.
FIT50 = FIT at a cut-off level of 50 ng Hb/ml; FIT75 = FIT at a cut-off level of 75 ng Hb/ml; FIT100 = FIT at a cut-off level of 100 ng Hb/ml

Sensitivity proximal versus distal neoplasia

Eight participants were detected with CRC: two CRCs were detected in the proximal colon and six in the distal colon. The two proximal CRCs were detected at all respec-

tive cut-off levels. In contrast, five of six distally located CRCs (83%) were detected at the 50 ng/mL cut-off level and four at 75 and 100 ng/mL (67%).

Twenty-nine participants had proximally located advanced adenomas and 84 participants had distal advanced adenomas. Of the 119 participants with advanced neoplasia (advanced adenoma and CRC together), 31 participants had proximal advanced neoplasia and 88 distal advanced neoplasia. Twelve participants had both proximally and distally located advanced neoplasia. Isolated proximal advanced neoplasias were detected in 24 of 1,256 participants (1.9%). Of these, 9 (38%) were positive at a cut-off level of 50 ng/mL. Of the 83 participants with isolated distal advanced neoplasia, 31 (37%) were detected at a cut-off level of 50 ng/mL (p=0.99 for sensitivities proximal versus distal). At a cut-off level of 75 ng/mL, the sensitivity in detecting proximal and distal advanced neoplasia was 33% and 31%, respectively (p=0.85). At a cut-off level of 100 ng/mL these numbers were 33% and 29%, respectively (p=0.68).

DISCUSSION

We estimated the sensitivity, specificity and predictive values of a FIT (OC-Sensor) in detecting CRC, advanced adenomas and advanced neoplasia at different cut-off levels measured against colonoscopy within a randomized invitational population-based colonoscopy screening program. Almost 9 out of 10 screenees with CRC, 3 to 4 out of 10 with advanced adenoma, and 4 out of 10 with advanced neoplasia were detected using a single FIT at a low cut-off of 50 ng/ml. One out of twenty participants with a positive test result had CRC while a negative test result almost ruled out CRC. The sensitivity in detecting proximal advanced neoplasia was found to be similar to the sensitivity for distal advanced neoplasia. The importance of these data lies in particular in the sensitivity and negative predictive values of FIT for CRC and advanced adenoma.

This study has several strengths. All participants in this accuracy study were screening-naïve participants within a randomized invitational population-based primary colonoscopy screening trial. They were consecutively invited to perform FIT. This way, we were able to estimate accuracy of FIT measured against colonoscopy. This setting in a screening-naïve population is relevant as previous screening is likely to lower the prevalence of advanced lesions in a screening population, which may interfere with test performance and in particular yield lower positive predictive values.(21) The detection rates in our screening-naïve population may be higher than in a population who had received previous screening. Detection rates for CRC (0.6%) and advanced neoplasia (9%) were similar to those reported in previous studies performed in asymptomatic European populations.(22-24) Endoscopists were blinded for the FIT re-

sult, which prevented investigator bias. Research staff attended all colonoscopies and prospectively recorded all data on colonoscopy quality indicators and polyp detection ensuring accurate and optimal data-collection. Polyps were evaluated by two expert gastro-intestinal pathologists to minimize inter-observer bias. All FITs were collected and adequately processed within 48 hours after performing the test, minimizing but not eliminating the risk of hemoglobin degradation.

Some limitations should be acknowledged. Our study population consisted of participants who participated in primary colonoscopy screening. Only 22% of all invitees decided to participate in colonoscopy screening.(16) This low participation rate mirrors other studies and programs in Europe.(24;25) This limits the accuracy of FIT compared to a FIT based invitational population screening program. Participation in FIT-screening is higher than in colonoscopy screening: 60 to 62% in pilot studies.(10;11) This limited participation rate may have resulted in a study group with a different CRC risk-profile compared to FIT-screening. It is possible that participants in more invasive screening programs are more likely to have unreported CRC symptoms, which would increase the positive predictive value of FIT. The majority of our study group was caucasian. The prevalence of colonic polyps seems to differ between ethnic populations which could affect FIT accuracy.(26) Next, our reference standard, colonoscopy, is not infallible. A meta-analysis of back-to back colonoscopies has shown that approximately 2% of large adenomas will be missed during colonoscopy.(27) Colonoscopy has also shown to miss right-sided neoplasia.(28;29) Both could have had a positive (missed lesions in FIT-negatives) or negative (missed lesions in FIT-positives) impact on the observed FIT performance. Lastly, we estimated FIT accuracy in only one round of FIT-screening. We therefore underestimate the sensitivity of FIT compared to FIT-sensitivity of an entire annual or biannual FIT screening program.

We decided not to exclude participants with an incomplete colonoscopy, as such exclusion can introduce bias. Colorectal neoplasia can still be detected in patients with an incomplete colonoscopy and exclusion should then be erroneous (7 out of 21 participants with an incomplete colonoscopy were detected with an adenoma and received subsequent follow-up or surveillance by colonoscopy or CT-colonography). Our results reflect daily practice and we demonstrated high standard colonoscopy quality parameters. Besides, an additional analysis among participants with a complete colonoscopy provided similar FIT accuracy results.

Study participants brought the FIT to their scheduled screening colonoscopy or our research staff collected it at home. In a common screening setting, the FIT is returned by mail which may cause delay. This could affect test accuracy, in particular with higher ambient temperatures.(30) Our strategy, ensuring rapid FIT sample return, may have affected test accuracy in a positive way.

Although a significant number of advanced lesions were identified, we only detected 8 screenees with CRC and 24 and 83 screenees with isolated proximal and distal advanced neoplasia. This limits the precision of our estimates of FIT sensitivity in CRC detection, and our comparison of FIT sensitivities in detecting proximal and distal advanced neoplasia.

To our knowledge, this is the first study evaluating the accuracy of FIT within an invitational population-based colonoscopy screening program. Other studies comparing FIT and colonoscopy included participants of non-invitational screening programs. In such programs, the proportion of participants with a positive CRC family history was higher compared to our study (13-14% versus 3%).(22;31) This implies that participation may have been triggered by other factors, such as abdominal symptoms or a positive CRC family history. We estimated a sensitivity of 38% in detecting advanced neoplasia and 88% for CRC at the lowest cut-off level. Two German studies reported on the performance of several FITs in non-invitational colonoscopy screening.(23;32) At 95% specificity, they reported a sensitivity of 33% for detecting advanced adenomas using an ELISA-based (Ridascreen) quantitative FIT.(32) They also showed that this type of FIT had a similar sensitivity compared to six qualitative FITs at defined levels of specificity.(23) Other studies that also compared FIT with colonoscopy findings reported on non-population based average-risk cohorts and used other FIT types including qualitative tests.(33;34) A Korean study reported on 770 subjects, who performed three FITs (OC-Sensa Micro; Eiken Chemical, Tokyo, Japan) from three consecutive bowel movements prior to colonoscopy.(35) They reported a relatively high positivity rate (12%), a high sensitivity in detecting advanced neoplasia (47%) but a low specificity (91%) compared to our study. Taking only the first FIT into account, the observed sensitivities and specificities were similar to our study. We asked participants to perform one sample of FIT which ruled out possible confusion over different FIT samples. Our design rather mimicks a FIT screening program as one sample is advised in most population-based screening programs. However we know from previous experience that repeat FIT testing increases diagnostic yield of advanced lesions.(36)

We estimated similar sensitivities for detecting proximal and distal advanced neoplasia: 38% versus 37%. This implicates that FIT may be a good screening strategy for preventing both proximal and distal CRC. In contrast, two other studies reported a lower sensitivity in detecting proximal advanced neoplasia than for distal advanced neoplasia: 20% versus 33% and 16% versus 31%, respectively.(33;37) These contrasting results may be explained by the fact that the study population in our invitational population-based screening differed from the Japanese hospital-based screening and from the German non-invitational population based study. We also used another type of FIT (OC-Sensor) compared to the other studies (respectively Magstream and Ridascreen).(33;37) It is conceivable that the type of FIT we used was relatively more

capable of detecting proximal advanced neoplasia than other types. The different cut-off levels may be postulated as a potential explanation for the different results, but this is not supported by the literature. The German group reported significant differences in detecting proximal and distal advanced neoplasia at cut-off levels of 2, 8 and 15 microgram hemoglobin per gram feces. At a cut-off level of 15 microgram hemoglobin per gram feces, the one with which we can compare, we found a similar FIT sensitivity in detecting proximal and distal advanced neoplasia. The differences could also to some extent be influenced by the quality of the follow-up colonoscopy, In recent years, attention for missed neoplasia in the proximal colon has grown which increases awareness among endoscopists for adequate inspection of the proximal colon. If proximal advanced neoplasias had predominantly been missed in FIT-positives, this could be an explanation for the lower sensitivity in detecting proximal advanced neoplasia in these studies. Comparable sensitivity in detecting proximal and distal advanced neoplasia indicates that hemoglobin degradation on passage to the anus only has only a minimal effect on the accuracy of FIT.

In most cost-effectiveness analyses, FIT sensitivity was simulated in the absence of population-based data on colonoscopy in FIT-negatives. In a recent cost-effectiveness analysis, a distinction was made between sensitivity in detecting CRC long before it became clinical and shortly before it became clinical.(38) FIT sensitivity in detecting CRC long before clinical was assumed to be 61%, 56% and 51% at a cut-off level of 50, 75 and 100 ng/mL, respectively. FIT sensitivity in detecting CRC shortly before clinical was assumed to be 88%, 86% and 83% respectively. We detected 5 CRCs Dukes A, 1 Dukes B and 1 Dukes C and found FIT sensitivities for detecting CRC of 88% (50 ng/mL) and 75% (75 and 100 ng/mL). Assuming that most subjects with Dukes A carcinoma may be detected by colonoscopy screening long before they become symptomatic, our results indicate a higher FIT sensitivity than previously assumed. Per-lesion sensitivities for detecting advanced adenomas were assumed to be 16.7%, 15.2% en 13.0% at cut-off levels of 50, 75 and 10 ng/mL, respectively, which is substantially lower compared to the results in this study. Our results can be used as input in cost-effectiveness analyses.

This study provides further significant evidence to overturn the general belief that FIT tests like gFOBT only detect colorectal cancer, but not advanced adenomas under the assumption that these do not bleed. In a previous study comparing gFOBT and FIT screening, we found that gFOBT led to detection of 6 subjects with advanced neoplasia per 1000 screenees invited, whereas FIT screening led to detection of 21 per 1000.(11) The increased yield in particular comprised of screenees with an advanced adenoma. This is supported by our current finding that FIT screening in particular at low cut-off detects a sizeable proportion of subjects with advanced adenoma. Repeated screening rounds are then necessary to increase this proportion as well as population coverage as subjects who did not participate in the first round may

participate with repeat screening. On the other hand, other studies suggested that adenomas that did not bleed at the time of a screening round and were missed, may have a higher than average probability of not bleeding in a next screening round and therefore remain undetected.(38;39) More data of follow up rounds are necessary to quantify such an expected effect.

We showed that raising the cut-off level from 50 to 75ng/mL or even to 100 ng/mL resulted as expected in a lower sensitivity, but in a higher specificity in detecting CRC or advanced neoplasia. Although a higher cut-off value would result in a higher number of missed lesions, it may be necessary to adapt the cut-off level to the available colonoscopy capacity and investment resources in a certain region. A recent study showed that adapting the cut-off level was the most optimal strategy to meet decreasing colonoscopy capacity.(14) Though, the cost-effectiveness analysis by Wilschut *et al.* showed that a cut-off level of 50 ng/mL is most cost-effective.(38) The lower specificity at a cut-off level of 50 ng/mL (compared to higher cut-off levels) was outweighed by the fact that fewer screening rounds were sufficient to be equally effective.

Depending on colonoscopy capacity and costs, it is also possible to perform more than one sample of FIT. The Korean study showed that the sensitivity of FIT rose from 33% to 47% by using three FITs instead of one FIT sample.(35) A Dutch randomized trial showed that the positivity rate of FIT increased from 8% to 13% by adding a second FIT sample, although the detection rate did not differ significantly.(36) Lowering the cut-off level or raising the number of tests will result in a higher sensitivity and a lower specificity of FIT. Although a higher proportion of participants with advanced neoplasia will be detected by FIT, it will yield a higher number of positive screenees and require more colonoscopies. The corresponding higher number of false positives may burden screening participants by conducting unnecessary colonoscopies.

We report on the accuracy of a once-only FIT with colonoscopy as the clinical reference standard. Repeated screening rounds will increase the yield of FIT. A recent two-round FIT study looking at intervals of 1, 2, and 3 years, showed that the yield at the second screening round was not influenced by the interval length within this one to three year range.(40) Further studies need to be done to find the optimal interval for repeat FIT screening.

In conclusion, this study shows that FIT has a high sensitivity in the detection of CRC and a moderate sensitivity in detecting advanced neoplasia within an invitational colonoscopy screening program. In contrast to previous findings, the sensitivity of FIT in detecting proximal and distal advanced neoplasia is equal.

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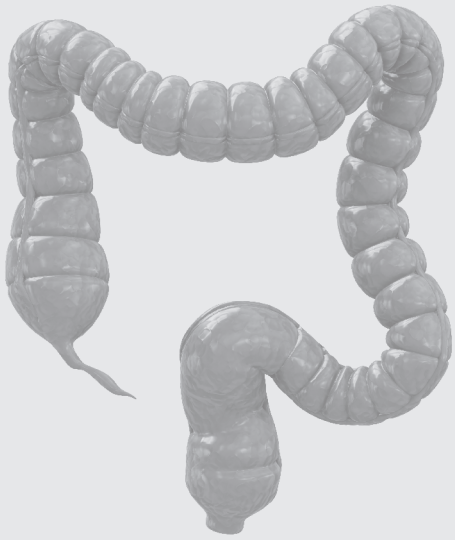
Appendix 1: Colonoscopy findings at different FIT cut-off levels

	All	FIT ≥ 50	FIT < 50	FIT ≥ 75	FIT < 75	FIT ≥ 100	FIT < 100
	n=1,256	n=121	n=1,135	n=88	n=1,168	n=71	n=1,185
≥ *1 AA**	113	40	73	35	78	33	80
	9%	33%	6%	40%	7%	47%	7%
≥ *1 CRC*	8	7	1	6	2	6	2
	0.6%	6%	0.1%	7%	0.2%	9%	0.2%
≥ *1 AN**	119	45	74	39	80	37	82
	9%	37%	7%	44%	7%	52%	7%

AA = advanced adenoma; CRC = colorectal carcinoma; AN = advanced neoplasia
Cells contain number of participants and percentages
FIT ≥ [50,75,100] = Percentage and number of participants with FIT cut-off level equal or higher than [50,75,100]
FIT < [50,75,100] = Percentage and number of participants with FIT cut-off level lower than [50,75,100]
* 2 participants with CRC in addition had one or more advanced adenomas

CHAPTER 7

Differences in Proximal Serrated Polyp Detection among Endoscopists are Associated with Variability in Withdrawal Time



T. R. de Wijkerslooth, E. M. Stoop, P. M. Bossuyt, K.M.A.J. Tytgat, J. Dees, E.M.H. Mathus-Vliegen, E. J. Kuipers, P. Fockens, M. E. van Leerdam, E. Dekker

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ABSTRACT

Background: Insufficient detection of proximal serrated polyps (PSP) might explain the occurrence of a proportion of interval carcinomas in colonoscopy surveillance programs.

Objective: To compare PSP detection between endoscopists and to identify patient and endoscopist-related factors associated with PSP detection.

Design: Prospective study in unselected patients.

Setting: Colonoscopy screening program for colorectal cancer at two academic medical centers.

Patients: Asymptomatic consecutive screening participants (50 to 75 years).

Interventions: Colonoscopies were performed by five experienced endoscopists. All detected polyps were removed. Multiple colonoscopy quality indicators were prospectively recorded.

Main outcome measurements: We compared PSP detection between endoscopists by calculating odds ratios (OR) with logistic regression analysis. Logistic regression was also used to identify patient features and colonoscopy factors associated with PSP detection.

Results: 1,354 subjects underwent a complete screening colonoscopy: 1,635 polyps were detected, of which 707 (43%) were adenomas and 685 (42%) were serrated polyps including 215 PSPs. In 167 patients (12%) one or more PSP were detected. The PSP detection rate differed significantly between endoscopists ranging from 6% to 22% ($p<0.001$). Longer withdrawal time (OR 1.12; 95% CI: 1.10 to 1.16) was significantly associated with better PSP detection, while patient age, gender and quality of bowel preparation were not.

Limitations: Limited number of highly experienced endoscopists.

Conclusions: The PSP detection rate differs among endoscopists. Longer withdrawal times are associated with better PSP detection, but patient features are not (Clinical trial registration number: NTR1888).

Take-home message: PSP detection is not so much patient related, but depends more on the skills of the endoscopist, such as withdrawal time.

INTRODUCTION

Colonoscopy has been recommended by the American College of Gastroenterology as the preferred strategy for colorectal cancer screening of average risk individuals.(1) Colonoscopy is considered the most accurate method for the detection of colorectal neoplasia. Although its ability to identify left sided neoplasia is undisputed, this is less so for proximally located cancer. (2;3) This can be explained by several factors. First, colonoscopies can be inadequate because of lack of cecal intubation or appropriate bowel preparation.(3) Insufficient detection and removal of serrated polyps could be another explanation. Such polyps can develop into cancer through the serrated pathway, one that differs from the traditional adenoma-carcinoma sequence and is characterized by *BRAF* mutations and CpG island methylator phenotype (CIMP).(4-8) Previous studies have demonstrated an association between proximal location of serrated polyps and synchronous advanced neoplasia and colorectal cancer, implying a higher risk of advanced neoplasia during surveillance.(9;10)

Serrated polyps may be more easily missed during colonoscopy because of their flat morphology and ambiguous colour. This can be the case particularly in the proximal colon where the endoscopic view is often blurred because of insufficient bowel preparation. Serrated polyps also have traditionally been thought to be benign. Endoscopists may therefore be unaware of their malignant potential and decide not to remove these lesions during colonoscopy. Kahi et al. have shown that proximal serrated polyp detection varies among endoscopists.(11) Because of the retrospective design of their study they were unable to evaluate the effect of potential confounders on polyp detection, in particular the quality of the bowel preparation.

We have performed a prospective study in unselected patients to compare detection of proximal serrated polyps among endoscopists in a primary colonoscopy screening program for colorectal cancer, and to evaluate associations between proximal serrated polyp detection and patient related and endoscopist related factors. In addition, we also compared the effect of these factors on the detection of adenomas.

METHODS

Study population

Data were collected in the randomized, multicenter Colonoscopy or Colonography for Screening (COCOS) trial. The overall design of this invitational population based colorectal cancer screening program, as well as its main results (participation and diagnostic yield), have been described in detail elsewhere.(12;13) Screening participants allocated to the colonoscopy arm were included for this study. Between June

2009 and July 2010, a total of 6,600 asymptomatic individuals of the Amsterdam and Rotterdam region were randomly selected and invited for colonoscopy screening.

Patients with an end-stage disease were excluded, as were individuals who had been scheduled for surveillance colonoscopy, because of a personal history of colorectal cancer, colon adenomas or inflammatory bowel disease, as well as those who had undergone a full colonic examination in the previous 5 years with either a complete colonoscopy, CT colonography and/or double contrast barium enema.

The study was discussed during a pre-colonoscopy consultation, after which participants were invited to sign informed consent. Next, consenting eligible participants were scheduled for a primary screening colonoscopy. Ethical approval was obtained from the Dutch Health Council (2009/03WBO, The Hague, The Netherlands). The trial was registered in the Dutch Trial Register: NTR1829 (www.trialregister.nl).

Colonoscopy and histopathology

All colonoscopies were performed at the Academic Medical Center in Amsterdam and Erasmus University Medical Center in Rotterdam by senior gastroenterologists with an experience of at least 1,000 colonoscopies each in their careers. Each gastroenterologist performed all his/her colonoscopies at one center. Colonoscopies were recorded on DVD and performed according to the standard quality guidelines defined by the Society of Gastrointestinal Endoscopy.(14) Colonoscopes were 160 or 180 series variable stiffness instruments (Olympus Medical Systems, Tokyo, Japan). Participants received 2L of polyethylene electrolyte glycol solution (Moviprep; Norgine bv, Amsterdam, The Netherlands) and 2L transparent fluid, split-dose or single dose, dependent on time of procedure (morning or afternoon).

Research staff prospectively recorded a number of colonoscopy variables, including cecal intubation time, withdrawal time, endoscopist, field of view of the colonoscope (140° or 170°), definition of the colonoscope (high or low), use of a plastic cap at the tip of the colonoscope, timing of the colonoscopy (morning/afternoon), use of sedation (midazolam and/or fentanyl), use of antispasmodic medication (butylscopolamine) and quality of the bowel preparation. Quality of the bowel preparation was assessed by the validated Ottawa bowel preparation score, which includes three segment scores (0-4) and an overall score (0-2) and ranges from 0 (excellent bowel preparation in all three colonic segments) to 14 (very poor bowel preparation).(15) Endoscopists were instructed to intubate the cecum and to document the cecal landmarks (cecal valve and appendix orifice or intubation of terminal ileum). Withdrawal time was recorded by a stopwatch and was demanded to be at least six minutes, after subtracting the time needed for polypectomies. Polyps were directly removed during withdrawal and obtained for histological assessment. Polyp variables were prospec-

tively recorded including location, size and morphology (pedunculated, sessile, flat). Proximal location was considered as proximal to the splenic flexure.

All polyps were evaluated by two expert gastro-intestinal pathologists, one in each center. Serrated polyps included hyperplastic polyps, sessile serrated lesions and traditional serrated lesions. Adenomas were classified as tubular, tubulovillous or villous; dysplasia was assessed as either low or high grade.(16) An advanced adenoma was defined as an adenoma $\geq$ 10 mm, $\geq$ 25% villous or with high grade dysplasia. Advanced neoplasia comprised advanced adenoma and CRC altogether.

Outcome measures and statistical analysis

First, we compared proximal serrated polyp detection among endoscopists with logistic regression analysis. The outcome variable was the detection of one or more proximal serrated polyps in a per-patient analysis. Endoscopists were included in the model using dummy variables, by using the endoscopist with the highest detection rate as the reference. To adjust for potential confounders, we also included patient's age, gender and quality of the bowel preparation in the logistic regression model. Intubation times and withdrawal times were compared among endoscopists by the Kruskal-Wallis test statistic.

Next, we intended to identify patient features and colonoscopy factors associated with the detection of one or more proximal serrated polyps in a per-patient analysis. We expressed the strength of the corresponding associations as odds ratios and estimated these using univariable and multivariable logistic regression analysis, once again using detection of a proximal serrated polyp as the outcome variable. We considered factors that may affect polyp detection as described in the literature. We evaluated the following patient-related factors: age (17), gender (17) and the quality of the bowel preparation.(18) We also evaluated these colonoscopy-related factors: intubation time (19), withdrawal time (20), field of view of the colonoscope (140° or 170°) (21), definition of the endoscope (high or low) (22;23), use of a plastic cap (24), timing of the colonoscopy (morning/afternoon) (25), use of sedation (midazolam and/or fentanyl) (26), use of antispasmodic medication (butylscopolamine) (27) and Gloucester comfort score (28). We evaluated the same variables in a different set of logistic regression models, to estimate the strength of the corresponding associations with the detection of adenomas in the entire colon.

In all analyses we only included data from endoscopists who performed more than 50 colonoscopies in this study. We excluded participants with an incomplete colonoscopy, that is, those in which the cecum was not intubated because we could not assess detection of proximally located polyps and/or other quality indicators. Two-sided p-values of less than 0.05 were considered to indicate statistically significant differences. All analyses were performed by using PASW statistics version 18.0 for Windows.

Sample size calculation

The sample size calculation for the randomized trial in which this study was embedded is described in detail elsewhere.(12;13). With approximately 1400 colonoscopies, and assuming a baseline detection rate of about 12%, we would have at least 80% power to detect an odds ratio of 1.53 for dichotomous variables in the logistic regression (at a 50% prevalence; 1.67 at a 20% prevalence), or an odds ratio of 1.3 for a change in one standard deviation from the mean in continuous variables.

RESULTS

A total of 1,426 invitees participated in the colonoscopy screening program of whom 1,407 (99%) underwent a complete screening colonoscopy. In this group, 1,354 colonoscopies were completed by endoscopists who had performed more than 50 colonoscopies. Of the corresponding study participants, 689 (51%) were men; their median age was 60 years (IQR 55 to 65 years). The median Ottawa bowel preparation score was 5 (IQR 3 to 8). The median net withdrawal time was 10 minutes (IQR 8 to 15 minutes).

Overall, 1,635 polyps were detected of which 707 (43%) were adenomas and 685 (42%) were serrated polyps. The mean number of adenomas per patient was 0.52 (SD 1.08). The mean number of serrated polyps per patient was 0.51 (SD 1.16). Of the detected serrated polyps, 215 (31%) were proximally located. These were detected in 167 patients (12%). The mean number of proximal serrated polyps per patient was 0.16 (SD 0.48). The median proximal serrated polyp size was 4 mm (IQR 3 to 7). In 392 patients (29%) one or more adenomas were detected. The median adenoma size was 4 mm (IQR 3 to 7). An advanced adenoma was detected in 119 patients (9%) and advanced neoplasia in 125 patients (9%).

Table 1: Endoscopist's adenoma detection rates (ADR) and proximal serrated polyp (PSPR) detection rates

Endoscopist	Colonoscopy experience (years)	Number of colonoscopies in the study	Intubation time (median, IQR)	Withdrawal time (median, IQR)	ADR	PSPR	Odds ratio	95% CI
Endoscopist 1	9	147	13 (9-17)	16 (13-20)	33%	22%	1	N/A
Endoscopist 2	30	192	8 (6-12)	16 (13-20)	37%	20%	0.85	0.50-1.44
Endoscopist 3	9	310	7 (5-11)	9 (7-12)	30%	16%	0.65	0.40-1.06
Endoscopist 4	6	52	9 (6-13)	11 (9-15)	40%	15%	0.63	0.27-1.57
Endoscopist 5	35	653	5 (4-8)	8 (7-10)	24%	6%	0.22	0.13-0.36

Differences among endoscopists

There were significant differences among endoscopists in PSP detection rates (p<0.001) and adenoma detection rates (p=0.002), as summarized in **Table 1**. Among experienced endoscopists, the PSP detection rate varied from 6% to 22%; the adenoma detection rate varied from 24% to 40%. These differences also were observed when we adjusted for differences in case-mix. When we included patient's age, gender and quality of the bowel preparation the differences among endoscopists were significant (p<0.001 and p=0.001, for PSP detection and adenoma detection respectively). Median intubation times differed significantly among endoscopists (p<.001); ranging from 5 to 13 minutes. Median withdrawal times were also significantly different (p<0.001); these varied from 8 to 16 minutes. The endoscopist with the highest PSP detection rate was third in adenoma detection. The endoscopist with the highest adenoma detection rate was fourth in PSP detection.

Factors associated with proximal serrated polyp and adenoma detection

Associations between patient-related and procedure-related factors and the detection of proximal serrated polyps (PSP) and adenomas are summarized in **Table 2**. Significantly more adenomas were detected in elderly patients, in males and in patients with better bowel preparation. Including the proximal bowel preparation score instead of overall bowel preparation scores in an alternative multivariable model for PSP detection showed comparable results.

Of the procedure-related factors, withdrawal time was significantly associated with adenoma detection: more adenomas were detected in patients with longer withdrawal times. Adenoma detection differed significantly among subgroups defined by the Gloucester comfort score but no linearity was observed between higher adenoma detection and increasing discomfort. Use of butylscopolamine was associated with better adenoma detection in the univariable analysis; when we adjusted for case-mix this effect was no longer observed.

PSP detection was found to be associated with intubation time, withdrawal time and use of butylscopolamine in the univariable analysis. These factors were no longer significant when taking patient factors and all colonoscopy factors into account. In the multivariable analysis, withdrawal time was the only factor significantly associated with PSP detection: PSP detection was significantly more likely during procedures with longer withdrawal times.

Association of proximal serrated polyp detection and adenoma detection

Associations were observed between PSP detection and detection of colorectal neoplasia in the entire colon. In the univariable analysis, better PSP detection was associated with higher adenoma detection (OR 1.73; 95% CI 1.23 to 2.41; p=0.001),

Table 2: Factors associated with the detection of proximal serrated polyps (PSP) and adenomas (AD)

Factor	PSP detection						Adenoma detection					
	Univariable			*Multivariable*			*Univariable*			*Multivariable*		
	OR	95% CI	*p-value*	OR	95% CI	*p-value*	OR	95% CI	*p-value*	OR	95% CI	*p-value*
Patient-related factors												
Age (years)	1.00	0.98-1.03	.85	0.98	0.95–1.01	.26	1.06	1.04-1.08	<.001	1.05	1.03-1.08	<.001
Gender (female)	1.10	0.80-1.52	.56	1.25	0.83–1.86	.27	0.65	0.52-0.82	<.001	0.68	0.51-0.91	.010
Ottawa score (0-14)*	0.96	0.91-1.02	.17	0.98	0.92-1.05	.52	0.95	0.92-0.99	.011	0.95	0.91-0.99	.041
Colonoscopy-related factors												
Intubation time (min)	1.05	1.02-1.07	<.001	1.01	0.98-1.04	.57	1.01	0.99-1.03	.40	0.99	0.96-1.02	.41
Withdrawal time (min)	1.10	1.08-1.13	<.001	1.12	1.10-1.16	<.001	1.11	1.09-1.13	<.001	1.12	1.09-1.15	<.001
Definition of colonoscope (high)	1.33	0.84-2.12	.23	1.07	0.45-2.53	.88	1.23	0.89-1.68	.21	1.10	0.57-2.12	.78
Field of view of colonoscope (170°)	1.10	0.74-1.63	.64	1.30	0.61-2.78	.50	1.25	0.94-1.66	.13	1.33	0.74-2.40	.34
Use of transparent cap (yes)	1.11	0.81-1.53	.52	1.20	0.83-1.75	.33	0.95	0.76-1.20	.69	0.95	0.72-1.24	.69
Use of midazolam and/or fentanyl (yes)	0.80	0.48-1.34	.39	0.88	0.48-1.61	.67	1.01	0.68-1.50	.96	1.10	0.70-1.74	.68
Use of butylscopolamine (yes)	0.61	0.44-0.85	.003	0.79	0.53-1.17	.23	0.75	0.60-0.95	.015	0.91	0.68-1.22	.51
Gloucester comfort scale**			.06			.17			.26			.040
1 or 2 moments of mild discomfort, tolerable	*0.65*	*0.44-0.96*		*0.85*	*0.54-1.35*		*1.00*	*0.76-1.33*		*1.43*	*1.02-2.00*	
Several moments of discomfort, tolerable	*0.85*	*0.54-1.36*		*0.88*	*0.50-1.53*		*1.24*	*0.89-1.74*		*1.77*	*1.17-2.68*	
Several moments of discomfort, hardly tolerable	*1.17*	*0.64-2.13*		*1.59*	*0.78-3.27*		*0.79*	*0.48-1.31*		*1.36*	*0.75-2.46*	
Frequent moments of extreme discomfort	*1.94*	*0.74-5.05*		*2.53*	*0.84-7.58*		*0.48*	*0.16-1.42*		*0.61*	*0.18-2.03*	
Timing of colonoscopy (afternoon)	1.13	0.81-1.56	.47	1.14	0.76-1.70	.52	1.14	0.90-1.44	.27	1.14	0.85-1.54	.38

* Ottawa score ranging from 0 (excellent bowel preparation in all three colonic segments) to 14 (very poor bowel preparation)
** Odds ratios relative to "no discomfort"

advanced adenoma detection (OR 2.43; 95% CI 1.53 to 3.84; p<0.001) and advanced neoplasia detection (OR 2.34; 95% CI 1.52 to 3.75; p<0.001). When we adjusted for patient features (age, gender and quality of bowel preparation), these associations were still observed. Better PSP detection was associated with higher adenoma detection (OR 1.74; 95% CI 1.23 to 2.46), advanced adenoma detection (OR 2.41; 95% CI 1.51 to 3.86) and advanced neoplasia detection (OR 2.37; 95% CI 1.49 to 3.76).

When we adjusted for patient features and colonoscopy factors, associations between PSP detection and detection of colorectal neoplasia (adenoma, advanced adenoma and advanced neoplasia) were no longer significant. In the multivariable analysis, including adenoma, advanced adenoma or advanced neoplasia detection, withdrawal time was the only factor consistently and significantly associated with PSP detection.

DISCUSSION

We performed a prospective study to compare proximal serrated polyp detection among endoscopists and to identify patient-related and procedure-related factors associated with the detection of proximal serrated polyps. PSP detection differed significantly among experienced endoscopists. In this population, we did not observe significant effects of age, gender or quality of the bowel preparation, but found withdrawal time to be strongly and significantly associated with PSP detection.

To our knowledge, this is the first prospective study to identify factors associated with PSP detection during colonoscopy. Our study population is relatively homogenous, because we included participants who all underwent a primary screening colonoscopy. Research staff attended all colonoscopies and prospectively recorded various data on the quality of the colonoscopy and polyp detection ensuring accurate and optimal data-collection. Polyps were evaluated by only two expert gastro-intestinal pathologists minimizing inter-observer bias. All colonoscopies were performed by experienced endoscopists who were instructed to remove all detected polyps.

We included all patient features and colonoscopy factors that may affect polyp detection as known to us from literature. It is possible that we failed to include all factors that could influence polyp detection. The limited number of participating endoscopists could be another limitation of our study. Because of the low number we could not evaluate factors on the endoscopist level, such as endoscopist's age, sex or technique. We cannot exclude an inter-observer variation in the distinction between serrated polyps and adenomas. A recent study in a screening population showed inter-observer agreement for non-adenomatous or adenomatous polyps in 96% of cases, with a very good corresponding kappa value of 0.88 (29). Applying

these findings to our study would suggest that inter-observer variation does not have a large effect. To minimize the risk of coincidental observations, we excluded 53 colonoscopies from our analyses because they had been performed by experienced endoscopists who completed less than 50 colonoscopies for this screening trial.

Adenoma detection rates of less than 20% are associated with a higher risk of interval cancer (30). Because of this, quality guidelines proposed this percentage as the lower achievable limit in average risk populations.(14;30) Our endoscopists had adenoma detection rates ranging from 24% to 40%, all thus fulfilling this quality condition. In line with the literature, age, sex, quality of bowel preparation and withdrawal time were associated with adenoma detection (17;18;20).

The endoscopists detected proximal serrated polyps in 12% of participants, but detection rates varied significantly between endoscopists, from 6% to 22%. A recent retrospective study by Kahi et al reported an overall PSP detection rate of 13%, ranging from 1% to 18% among individual endoscopists.(11) Because of the retrospective design, Kahi et al were not able to report on the influence of two important quality parameters for polyp detection: quality of the bowel preparation and withdrawal time.

In our study, net withdrawal time (corrected by subtracting the time taken for polypectomy) was associated with PSP detection; detection of at least one PSP was more likely in colonoscopies with longer withdrawal times. To our knowledge, no other studies identified withdrawal time as contributor to PSP detection. In the adenoma detection rate, the odds ratio for withdrawal time was comparable, with a similar confidence interval. This suggests that withdrawal time is equally powerful for predicting PSP detection as for adenoma detection.

Serrated polyps usually have a flat morphology and are identical in color to the normal mucosa. Detection of these lesions might further be hindered by a typical 'mucus cap', a coating of mucus over the surface. Adequate bowel preparation aids in adenoma detection and we postulated this also would be the case for PSP detection, especially because bowel preparation tends to be worst in the proximal colon. To our surprise, the quality of the bowel preparation was not significantly associated with PSP detection. Including an evaluation of the proximal bowel preparation score in our multivariable model for PSP detection, instead of overall bowel preparation scores, showed comparable results. It is possible that the mucus cap on the serrated polyp attaches some residual stool, attracting attention and highlighting the polyp, especially if the proximal colon is rinsed with water. If so, the endoscopist should be well trained in detecting serrated polyps and be made aware of the clinical importance to remove them. Our colonoscopies were performed by experienced endoscopists. They were aware that they were performing study colonoscopies and we emphasized the importance of removing all detected polyps in colorectal cancer screening.

Two previous studies have reported PSP detection not to depend on patient's age or sex, and the results of our study are consistent with this conclusion.(10;11) Schreiner et al. suggested that higher age was not associated with PSP detection because they classified a traditional serrated adenoma with dysplasia as an adenoma. They presumed that non-dysplastic serrated lesions progressed to traditional serrated adenomas with increasing age. Because they classified a traditional serrated adenoma with dysplasia as an adenoma, they presumed that serrated polyp detection was underestimated in the higher age groups. In contrast, we defined hyperplastic polyps, sessile serrated lesions and traditional serrated lesions all as serrated polyps and found comparable results. From this we conclude that PSP prevalence may be comparable across age groups, which suggests that the risk of developing CRC via the serrated pathway does not depend on age.

Detection of PSP was associated with the detection of adenoma, advanced adenoma and advanced neoplasia in the univariable analysis, as previously described. (10;11) When we adjusted for patient features and colonoscopy factors these associations were no longer significant. Withdrawal time was the only factor significantly associated with PSP detection. Other prospective studies should be performed evaluating the effect of colonoscopy factors on PSP detection to confirm our results.

PSP detection rates and adenoma detection rates differed among endoscopists. These differences can be explained by the inspection skills of the endoscopist. Besides withdrawal time, withdrawal technique could be responsible for the variation in PSP detection. Rex et al. showed that adenoma detection rate depended on four quality criteria of withdrawal technique: (1) examining the proximal sides of flexures, folds and valves, (2) cleaning and suctioning, (3) adequacy of distention, and (4) adequacy of time spent viewing.(31) Likely, endoscopists with high PSP detection rates have a better withdrawal technique compared to endoscopists with low PSP detection rates. Further studies are required to confirm this hypothesis. Alternatively, it may also be that detection of proximal serrated adenomas depends on training, recognition, and focus. In that respect, it is notable that our results in terms of a correlation between PSP detection and withdrawal time are driven by the low PSP detection rate for one, elderly endoscopist with extensive colonoscopy experience. Although it was not part of our study, it seems reasonable to speculate that simple training and emphasis on removal of PSP lesions would help to improve the PSP detection rate for such endoscopists without the need for longer intubation and withdrawal times.

Endoscopists with lower PSP detection rates should be encouraged to detect and remove all polyps. For these endoscopists, increasing awareness of the risk of PSP may be necessary and additional training to improve SP detection could be beneficial. It is presumable that low PSP detection rates are associated with a higher risk for interval cancer, similar to the association between low adenoma detection rates (lower than

20%) and the higher interval cancer risk (30). To our knowledge, such an association has never been described in the literature. Further studies are needed to determine the association between PSP detection rates and the risk for interval cancer. If so, it would be logical to include PSP detection rate as a separate quality indicator for colonoscopy.

Recent studies demonstrated that patients with large PSPs are at increased risk of synchronous and likely metachronous advanced neoplasia and CRC.(9;10;32) These results might even justify surveying patients with PSPs henceforth. Terdiman and McQuaid recently proposed surveillance intervals for patients with serrated polyps.(33) Such a proposal will burden surveillance programs, colonoscopy capacity and medical costs, and should be weighed carefully against the risk of these patients developing CRC. The magnitude of that risk has to be clarified in future research.

In summary, our results suggest that PSP detection is not patient related, but that it depends on the skills of the endoscopist to detect PSP. Better PSP detection rates can probably be achieved by a longer withdrawal time during colonoscopy.

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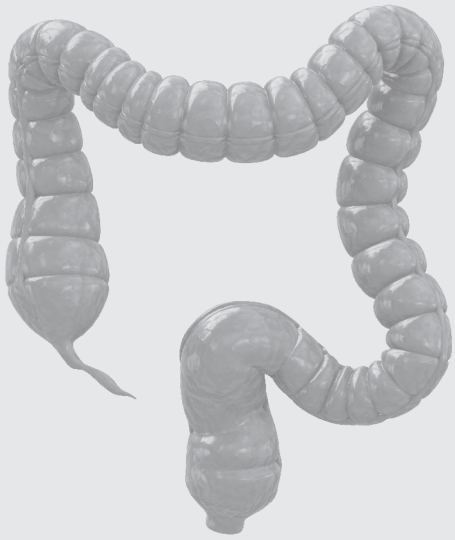
CHAPTER 8

Adenoma Detection with Cap-Assisted Colonoscopy versus Regular Colonoscopy: a Randomized Controlled Trial



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ABSTRACT

Objective: Conventional colonoscopy (CC) is considered the reference standard for detection of colorectal neoplasia, but it can still miss a substantial number of adenomas. The use of a transparent plastic cap may improve colonic visualization. We compared the adenoma detection of cap-assisted colonoscopy (CAC) to CC. Secondary outcomes were cecal intubation time, cecal intubation rate and the degree of discomfort of colonoscopy.

Design: This is a parallel, randomized, controlled trial at two centers. Asymptomatic participants, aged 50-75 years, in a primary colonoscopy screening program were consecutively invited. Consenting subjects were 1:1 randomized to either CAC or CC. All colonoscopies were performed by experienced endoscopists (≥ 1000 colonoscopies) who were trained in CAC. Colonoscopy quality indicators were prospectively recorded.

Results: A total of 1,380 participants were randomly allocated to CC (N=694) or CAC (N=686). Cecal intubation rate was comparable in the two groups (98% versus 99%; p=0.29). Cecal intubation time was significantly lower in the CAC group: 7.7±5.0 (mean±SD) with CAC versus 8.9±6.2 minutes with CC (p<0.001). Adenoma detection rates of all endoscopists were ≥20%. The proportion of subjects with at least one adenoma was similar in the two groups (28% versus 28%; RR 0.98; 95%CI 0.82-1.16), as well as the average number of adenomas per subject (0.49±1.05 versus 0.50±1.03; p=0.91). Detection of small size, flat and proximally located adenomas was comparable. CAC participants had lower Gloucester Comfort Scores during colonoscopy (2.2±1.0 versus 2.0±1.0; p=0.03).

Conclusion: CAC does not improve adenoma detection. CAC does reduce cecal intubation time by more than one minute and does lessen the degree of discomfort during colonoscopy.

What is already known about this subject?

- Conventional colonoscopy can miss a substantial number of adenomas.
- Cap-assisted colonoscopy (CAC) may improve colonic visualization and thus may improve adenoma detection.
- Currently, the possible improvement of adenoma detection by CAC is arguable as mixed results on polyp detection have been reported.

What are the new findings?

- CAC does not improve the detection of adenomas, nor the detection of small size, flat or proximally located adenomas.
- CAC does not improve the detection of adenomas in patients with a good bowel preparation.

- CAC does lessen the degree of discomfort during colonoscopy.

How might it impact on clinical practice in the foreseeable future?

- On the basis of our results, CAC should not be used in daily practice to improve the detection of adenomas.
- CAC can be used to reduce cecal intubation times and patient discomfort.

INTRODUCTION

Colonoscopy is widely accepted as the reference standard for detection of colorectal neoplasia. However, a substantial adenoma miss rate of 20 to 26% has been reported in tandem colonoscopy studies.(1) Forward viewing colonoscopes cannot visualize the full colonic surface and adenomas may be missed because they are located outside the visual field, hidden behind folds or flexures.(2)

The use of a transparent cap attached to the tip of a colonoscope may increase colonic surface visualization by depressing the colonic folds with the cap. In addition, a better endoscopic view can be created by keeping an appropriate distance between the tip of the colonoscope and the mucosa preventing a "red-out." This suggests that cap-assisted colonoscopy (CAC) may improve adenoma detection. A disadvantage of CAC, however, might be that de view is blurred if the bowel preparation is poor, as fecal material can remain in the cap.

So far, clear evidence that CAC improves adenoma detection is lacking. Previous studies did not report histopathology of all polyps, and / or did not achieve enough power to compare adenoma detection, and the results may have been influenced by investigator bias or by other confounders.(3-11) CAC has particular been studied in Asian populations. Mixed results on polyp and adenoma detection have been reported.(3-10) CAC trials in Western populations are limited; one small single center tandem study with only two participating endoscopists showed a reduction in adenoma miss-rates by CAC.(11) However, a recent meta-analysis could not draw any conclusions on the improvement of polyp or adenoma detection by CAC.(12) Regarding cecal intubation, CAC studies have demonstrated a shorter cecal intubation time and suggested easier cecal intubation by inexperienced endoscopists.(3;4) In addition, patient discomfort seems to be less during CAC.(5)

It is currently argued that an improvement in adenoma detection could possibly be achieved with CAC. We aimed to compare adenoma detection between CAC and conventional colonoscopy in a large two-center randomized controlled trial comprising screening naïve participants in a primary colonoscopy screening program. In addition, we compared cecal intubation time and rate, the degree of discomfort during colo-

noscopy, perceived burden of colonoscopy two weeks afterwards and complication rate. We prospectively recorded all colonoscopy quality indicators that could have affected adenoma detection. Several endoscopists participated in this study mimicking daily clinical practice of the effectiveness of CAC.

METHODS

Study population

Data were collected in the randomized, multicenter Colonoscopy or Colonography for Screening (COCOS) trial. The overall design of this invitational population based colorectal cancer screening program has been described in detail previously.(13) Between June 2009 and July 2010, 6,600 asymptomatic people from the Amsterdam and Rotterdam regions were randomly selected and invited for colonoscopy screening.

Subjects who had undergone a full colonic examination in the previous 5 years (complete colonoscopy, CT colonography and/or double contrast barium enema) were excluded from the screening program, as well as subjects planned for surveillance colonoscopy (personal history of CRC, colonic adenomas or inflammatory bowel disease (IBD)) and subjects with an end-stage disease. In addition, subjects with a (partial) colonic resection were excluded.

All screening participants scheduled for colonoscopy were invited to this randomized, parallel designed, study. After providing informed consent, eligible participants were randomly allocated 1 to 1 to either CAC or CC by a computerized randomization program (ALEA Randomization Service).(14) Randomization was stratified by age, sex and screening center using random block sizes of a maximum of six per block. It occurred within 24 hours prior to colonoscopy and was performed by the research staff. Participants and endoscopists were blinded for the randomization result until start of the colonoscopy. Ethics approval was obtained from the Dutch Health Council (2009/03WBO, The Hague, The Netherlands). The trial was registered in the Dutch Trial Register: NTR1888 (http://www.trialregister.nl).

Colonoscopy

Colonoscopies were performed at the Academic Medical Center Amsterdam and Erasmus Medical Center Rotterdam. Scheduled colonoscopies (CC or CAC) were consecutively performed in a morning or afternoon session according to the standard quality indicators defined by the Society of Gastrointestinal Endoscopy.(15) All colonoscopies were recorded on DVD. Colonoscopy variables were directly noted on a case record form by the research staff. All colonoscopies were performed by endoscopists with an experience of more than 1000 colonoscopies. They were trained in CAC and had an

experience of at least 20 cap-colonoscopies. Colonoscopes were CF-Q160 (140º field of view), CF-Q180 (170º field of view) and PCF-Q180 (140º field of view) series variable stiffness instruments (Olympus Medical Systems, Tokyo, Japan).

All participants received standard bowel preparation, which included a low-fiber diet and oral intake of 2 L of transparent fluid and 2 L of hypertonic polyethylene glycol solution (Moviprep; Norgine bv, Amsterdam, The Netherlands) at home. Procedures were performed with the subject under conscious sedation in combination with an analgesic if desired using intravenous midazolam and fentanyl.

Endoscopists intended to intubate the cecum as quickly as possible without performing polypectomies. Cecal intubation was confirmed by documentation of cecal landmarks (cecal valve and appendix orifice or intubation of terminal ileum). During withdrawal of the colonoscope the colonic mucosa was carefully inspected and all detected polyps were directly removed and obtained for histological assessment. Minimal withdrawal time (minus time for polypectomy) was at least six minutes. Size of all polyps was measured by the endoscopist using open biopsy forceps with a 7 mm span. Localization was considered proximal if proximal to the splenic flexure.

Discomfort during colonoscopy was scored by the research staff on the five-point Gloucester Comfort Score, with scores ranging from no discomfort to severe discomfort.(16) Bowel preparation was scored using the validated Ottawa bowel preparation score(17), ranging from 0 (an excellent bowel preparation in all three colonic segments) to 14 (a very poor bowel preparation). A good bowel preparation was defined as a total score of 7 or lower, including segment scores of 2 or lower. In case of insufficient bowel preparation (Ottawa score $\geq$ 11) the procedure was interrupted and rescheduled with the same endoscopist using the same allocated strategy, unless the participant refused to undergo repeat colonoscopy.

Cap-colonoscopy

For the CAC group, a transparent cap was fitted to the tip of the colonoscope so that it protruded 4 mm ahead of the tip of the colonoscope. We used a cap with a diameter of 13.4 mm (D-201-12704; Olympus Medical Systems, Tokyo, Japan) or 15.0 mm (D-201-14304; Olympus Medical Systems, Tokyo, Japan) depending on the diameter of the colonoscope that was chosen in each procedure. Some improvements were made over the cap used in previous CAC studies. A side hole on the cap was created for drainage of fluid and fecal material. In addition, the edge of the cap was rounded off to minimize mucosal damage and the material was made more transparent **(Figure 1)**.

Histopathology

Histopathology was processed and stained using standard methods and evaluated by two expert pathologists (one in each center) according to the Vienna criteria.(18)

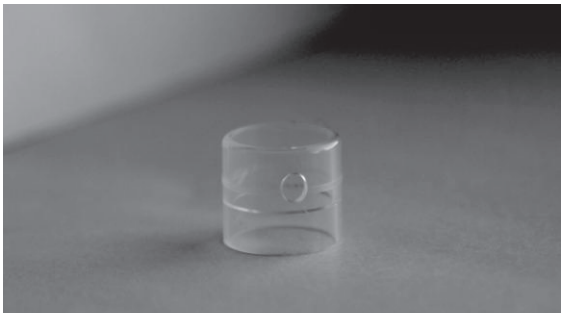

Figure 1: Cap used for the CAC arm.
A side hole on the cap was created for drainage of fluid and fecal material, the edge of the cap was rounded off to minimize mucosal damage and the material was made more transparent.

All lesions were classified into hyperplastic, serrated, tubular, tubulovillous, villous or carcinoma. Dysplasia was defined as either low grade or high grade. An advanced adenoma was defined as an adenoma $\geq$ 10 mm, $\geq$ 25% villous or with high grade dysplasia.

Complications

All acute complications were recorded at the time of the colonoscopy. Subjects were contacted two weeks after the procedure for registration of post-procedural complications. They were instructed to contact research staff if complications occurred in the following two weeks to ensure a complete complication registry of four weeks.

Questionnaire

All participants were asked to complete a questionnaire on perceived burden of the colonoscopy (PBQ) two weeks afterwards. It had been previously validated (13) It measured the perceived burden and pain of colonoscopy related items and of the full screening procedure (e.g. 'how burdensome/painful did you find insertion of the endoscope?'). All items were scored on five-point Likert scales (1=not at all; 2=slightly; 3=somewhat; 4=rather; 5=extremely).

Outcome measures and statistical analysis

The primary outcome measure was adenoma detection, defined as the proportion of participants with at least one adenoma (per-patient analysis). The number of adenomas per subject (per-polyp analysis) was defined as the total number of detected adenomas in each group divided by the total number of participants. Secondary outcomes were cecal intubation time and rate, the degree of discomfort during colonoscopy, perceived burden of the colonoscopy two weeks afterwards and complication rate.

We performed a subanalysis to investigate the influence of bowel preparation. We calculated adenoma detection rates in patients with good bowel preparation scores.

Adenoma detection was analyzed in an intention-to-treat and a per-protocol analysis. Adenoma detection was compared using the Chi-square test (per-patient analysis) and Mann-Whitney U test (per-polyp analysis) statistics. The Mann-Whitney U test statistic was used to compare procedural times and discomfort and perceived burden scores. The Chi-square test statistic was used to compare cecal intubation rate.

Two-sided P-values of less than 0.05 were considered to indicate statistically significant differences. All analyses were performed using SPSS version 16.0 for Windows. The results were reported using the CONSORT guidelines.(19)

Sample size:

In the conventional colonoscopy group, we expected that 20% of all subjects would have at least one adenoma, based on a large colonoscopy screening study.(20) We aimed to detect an increase in adenoma detection by 35%, resulting in an expected adenoma detection rate of 27% in the CAC group. A priori, we planned to scope a total number of *at least* 1,250 colonoscopies (625 per arm). With a two-sided test

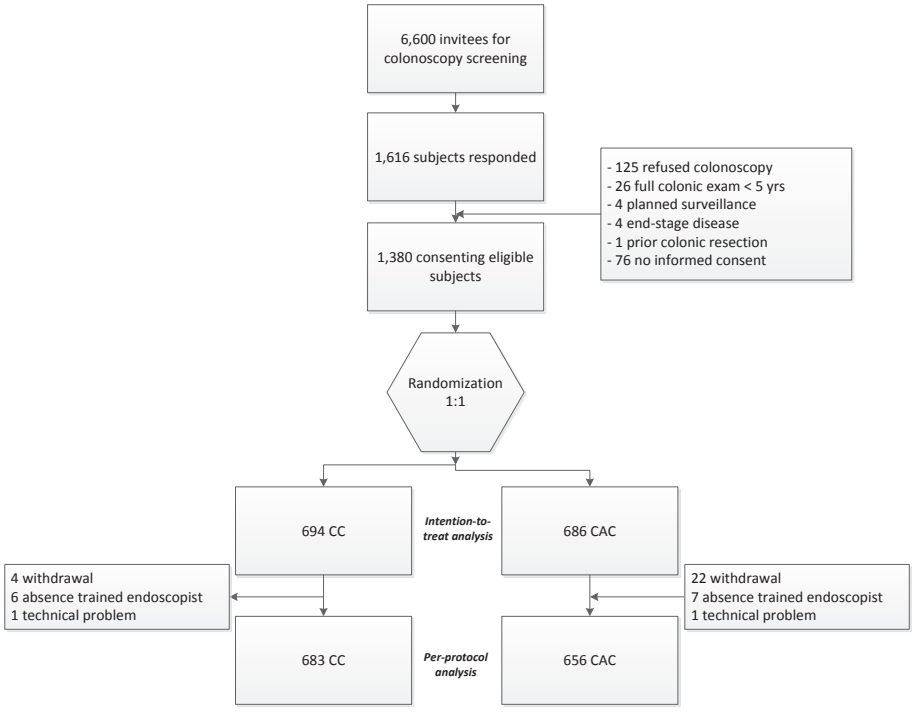

Figure 2: Patient flow

significance level of 0.05 we would achieve a power of at least 81% in detecting the indicated difference.

RESULTS

Figure 2 shows the patient flow. A total of 1,380 eligible screening participants consented and were 1:1 randomized to either conventional colonoscopy (CC) (n=694) or CAC (n=686). After randomization, a total number of 41 subjects dropped out because of withdrawal (n=26), absence of a trained endoscopist on the day of colonoscopy (n=13) or technical problems (n=2). As displayed in **Table 1**, groups were comparable with respect to age, gender or prior abdominal operation.

Table 1: Baseline demographics and colonoscopy characteristics

	CC (n=683)	CAC (n=656)	*P*-value
Age (yrs, median, IQR)	60 (55-65)	60 (55-65)	
Male (n, %)	346 (51%)	339 (50%)	
Prior abdominal operation (n, %)	203 (30%)	205 (31%)	
Diverticulosis	173 (25%)	144 (22%)	
Ottawa bowel preparation score (mean, SD)	5.5 (3.7)	5.8 (3.1)	
Sedation (n,%)			
None	69 (10%)	58 (9%)	
Midazolam only	1 (0%)	0 (0%)	
Fentanyl only	28 (4%)	25 (4%)	
Midazolam + Fentanyl	580 (86%)	570 (87%)	
No. colonoscopies each endoscopist (n, %)			0.41
Endoscopist 1	343 (50%)	311 (47%)	
Endoscopist 2	152 (22%)	146 (22%)	
Endoscopist 3	83 (12%)	97 (15%)	
Endoscopist 4	68 (10%)	74 (11%)	
Endoscopist 5	29 (4%)	25 (4%)	
Other endoscopists	8 (1%)	3 (1%)	
Colonoscope, 170° field of view	504 (77%)	477 (76%)	0.71
Colonoscope, high definition	541 (82%)	521 (83%)	0.82
Cecal intubation rate (n, %)	671 (98%)	649 (99%)	0.29
Cecal intubation time (minutes, mean, SD)	8.9 (6.2)	7.7 (5.0)	<0.001
Net withdrawal time (minutes, median, IQR)	10 (8-14)	10 (8-15)	0.64

Colonoscopy results

Almost all colonoscopies (1,328 of 1,339; 99%) were performed by five endoscopists who each performed at least 50 study colonoscopies **(Table 1)**. Each endoscopist performed a similar number of cap-colonoscopies and regular colonoscopies within this study. Colonoscopes with 140° and 170° field of view were used equally between the endoscopists. Cecal intubation was achieved in 671 of 683 subjects (98%) in the CC group versus 649 of 656 (99%) in the CAC group (p=0.29). Cecal intubation time was significantly lower in the CAC group than the CC group (7.7 ± 5.0 minutes with CAC versus 8.9 ± 6.2 minutes with CC; p<0.001). No significant differences were detected with respect to net withdrawal time or bowel preparation scores.

Polyp detection

In the intention-to-treat analysis, the proportion of participants with at least one adenoma was the same in the two groups (28% versus 28%; RR 0.98; 95% CI 0.82 to 1.16). The total number of detected adenomas per subject was not significantly

Table 2: Polyp detection conventional colonoscopy (CC) versus cap-assisted colonoscopy (CAC): per-protocol analysis

	CC (n=683)	CAC (n=656)	*P*-value
Total number of polyps	665	682	0.71
Total number of adenomas	339	341	0.92
Advanced adenomas	81	64	0.13
Total number of serrated adenomas	56	45	0.23
Total number of hyperplastic polyps	270	296	0.28
Adenomas per subject (mean, SD)	0.50 (1.06)	0.52 (1.05)	0.83
Advanced adenomas per subject (mean, SD)	0.12 (0.45)	0.10 (0.37)	0.34
Subjects ≥ 1 adenoma (n, %)	196 (29%)	189 (29%)	0.96
Subjects ≥ 1 advanced adenoma (n, %)	63 (9%)	51 (8%)	0.34
Size of all adenomas			
< 6 mm per subject (mean, SD)	0.32 (0.78)	0.36 (0.81)	0.35
6-9 mm per subject (mean, SD)	0.08 (0.35)	0.09 (0.34)	0.99
≥ 10 mm per subject (mean, SD)	0.09 (0.35)	0.07 (0.29)	0.18
Flat morphology			
Flat adenomas per subject (mean, SD)	0.02 (0.13)	0.02 (0.15)	0.49
Subjects ≥ 1 flat adenoma (n, %)	14 (2%)	16 (2%)	0.63
Proximal location			
Proximal adenomas per subject (mean, SD)	0.25 (0.69)	0.25 (0.71)	0.72
Proximal advanced adenomas per subject (mean, SD)	0.03 (0.19)	0.02 (0.19)	0.07
Subjects ≥ 1 proximal adenoma (n,%)	115 (17%)	104 (16%)	0.63
Subjects ≥ 1 proximal advanced adenoma (n,%)	22 (3%)	11 (2%)	0.07

different between CC and CAC (0.49 ± 1.05 versus 0.50 ± 1.03; p=0.91). In the CC group, 63 participants (9%) had at least one advanced adenoma versus 51 participants (7%) in the CAC group (RR 0.80; 95% CI 0.57 to 1.17). The total number of detected advanced adenomas per subject was also comparable between the groups (0.12 ± 0.45 versus 0.09 ± 0.36; p=0.27). The per-protocol analysis is displayed in **Table 2;** it showed comparable results.

Table 2 also shows size, morphology and location of all detected adenomas. Detection of small size (<6 mm) adenomas was comparable for CC and CAC, as well as the detection of 6-9 mm and large (>10 mm) adenomas. In addition, CAC did not detect a higher number of flat adenomas per subject or a higher number of subjects with flat adenomas. No significant differences between the groups were noted in the detection of proximal located adenomas.

Influence of endoscopist and bowel preparation on adenoma detection

Adenoma detection rates of all endoscopists are displayed in **Table 3**. One endoscopist who performed 54 colonoscopies in this study detected a lower number of subjects with at least one adenoma in the CAC group (55% versus 24%; p=0.02). Adenoma detection rates for all other endoscopists were not statistically different between CC and CAC.

We performed a subanalysis in patients with a good bowel preparation. In the CC group, 465 (68%) had at least a good bowel preparation versus 434 (66%) in the CAC group. The proportion of subjects with at least one adenoma was 30% in the CC group with a good bowel preparation versus 31% in the CAC group (p=0.92). The number of detected adenomas per subject was also comparable between the groups (0.55 ± 1.15 versus 0.56 ± 1.06; p=0.82).

Table 3: Adenoma detection rates of the different endoscopists

	No. colonoscopies	Subjects ≥ 1 adenoma (n, %) CC	CAC	*P*-value
Endoscopist 1	654	79 (23%)	78 (25%)	0.54
Endoscopist 2	298	45 (30%)	47 (32%)	0.63
Endoscopist 3	180	34 (41%)	30 (31%)	0.16
Endoscopist 4	142	20 (29%)	26 (35%)	0.47
Endoscopist 5	54	16 (55%)	6 (24%)	0.02
Other endoscopists	11	2 (25%)	2 (67%)	0.20

Discomfort during colonoscopy and perceived burden two weeks afterwards

In both groups, the majority of subjects received a combination of midazolam and fentanyl (**Table 1**). During colonoscopy, 21% in the CC group had "several moments of discomfort" versus 16% in the CAC group (**Figure 3**). Overall, Gloucester Comfort Scores were lower in the CAC group than in the CC group (mean score 2.0 ± 1.0 versus 2.2 ± 1.0; p=0.03).

Two weeks after colonoscopy, a total of 467 of 683 (68%) CC subjects returned the PBQ versus 483 of 656 (74%) subjects in the CAC group. The perceived burden and pain for colonoscopy related items (introduction of the colonoscope and proceeding the procedure including cecal intubation and withdrawal) two weeks after colonoscopy were scored comparably between the groups (**Figure 4**). The full procedure was

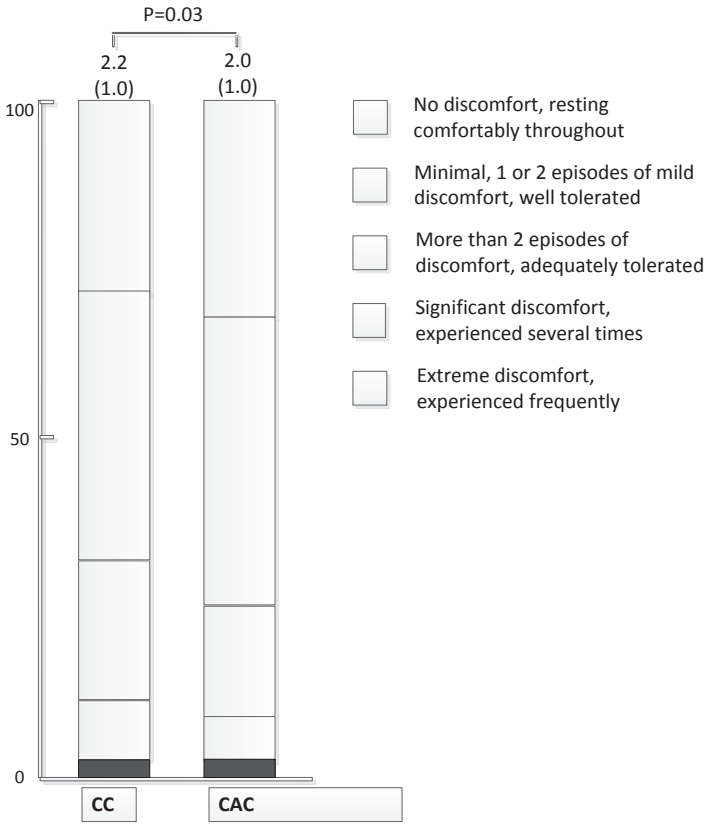

Figure 3: Discomfort during colonoscopy.
Discomfort during colonoscopy. This was measured by the Gloucester Comfort Score ranging from no discomfort (1) to extreme discomfort (5). On top of the bars, mean (SD) scores and significance levels between the groups are displayed.

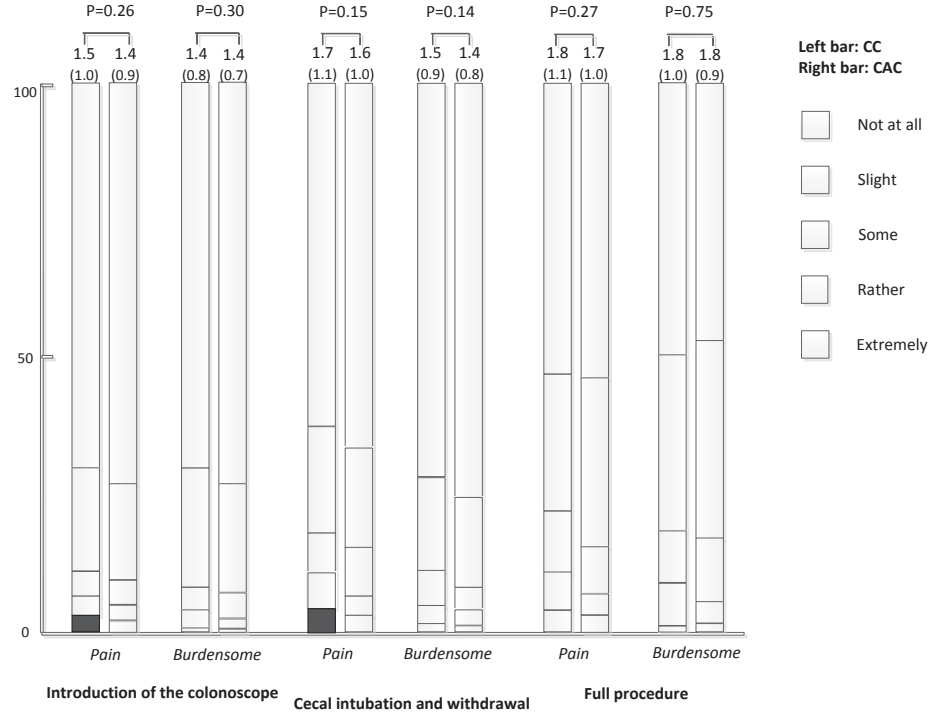

Figure 4: Perceived burden two weeks after the procedure.
Perceived pain and burden of different items and the full procedure was measured by a validated questionnaire. On top of the bars mean scores (SD) and significance levels between the groups are displayed.

perceived as not or slightly burdensome by 82% of CC participants and by 83% of CAC participants (mean score 1.8 ± 1.0 versus 1.8 ± 0.9; p=0.75) and perceived as not or slightly painful by 78% and 84% (mean score 1.8 ± 1.1 versus 1.7 ± 1.0; p=0.27), respectively. Two weeks after the colonoscopy, women had lower pain scores in the CAC than the CC group for proceeding the procedure (mean score 1.9 ± 1.3 versus 1.7 ± 1.1; p=0.04). Patients who did not receive sedation had comparable burden scores in both groups.

Complications

One post-polypectomy bleeding and one perforation occurred in the CC group versus none in the CAC group. One patient in the CC group died because of a spinal epidural abscess 23 days after the colonoscopy. In retrospect, this event was probably not related to the colonoscopy. Three non-colonoscopy related complications occurred in the CAC-group: pneumonia, urinary tract infection and atrial fibrillation.

DISCUSSION

We compared adenoma detection rates by CC and CAC in a population at average risk of colorectal cancer. We found that CAC did not improve the detection of adenomas nor the detection of small size, flat or proximally located adenomas. We also performed a subanalysis in patients with good bowel preparation scores showing similar results. CAC reduced cecal intubation times by more than one minute. In addition, CAC participants showed lower discomfort scores during colonoscopy.

This is the first large prospective randomized controlled trial adequately powered to compare adenoma detection between CC and CAC. Five experienced endoscopists with good adenoma detection rates and who were trained for CAC performed 99% of all colonoscopies. Our study population was uniform as all included participants underwent a primary screening colonoscopy. In addition, research staff attended all colonoscopies and prospectively recorded all data on polyp detection, procedural times and bowel preparation scores ensuring accurate and optimal data-collection. Conventional colonoscopies and cap-assisted colonoscopies were consecutively performed in a random order. Therefore, we believe that our results are reliable and applicable to daily clinical practice.

Unfortunately, we had to exclude 39 participants after randomization because of withdrawal from the study or absence of a CAC-trained endoscopist on the day of the procedure. Because of logistics, we had to randomize some participants one day before colonoscopy. Allocation to one of the two arms did not seem to be responsible for dropping-out since the result of randomization was only revealed to the patients and endoscopists just before the colonoscopy. More importantly, no significant differences were observed between the intention-to-treat and the per-protocol analysis. In our study, colonoscopes with different fields of view (140° and 170°) were used. This does not seem to have influenced the results as both types were used equally between the several endoscopists. In line with this, use of wideangle colonoscopes did not affect adenoma detection rates in previous studies.(21;22) Lastly, as blinding is not possible because the cap is visible on the monitor during colonoscopy, it is impossible to rule out an investigator bias in any study with the cap. Investigator bias would have been more likely if we had detected a higher number of subjects with adenomas in the CAC-group, as we aimed to improve adenoma detection by CAC.

According to quality guidelines, adenoma detection rates over 20% are required in populations at average risk of CRC.(15;23) Low adenoma detection rates are associated with an increased risk of interval colorectal cancer.(23) In our study, the endoscopists fulfilled this quality condition. Adenoma detection rates of the conventional colonoscopy group (control group) varied from 23% to 41% for those endoscopists performed more than 100 study colonoscopies. Good adenoma detection rates in

Table 4: Polyp and adenoma detection rates (per-patient and per-polyp analysis) in RCTs (CC versus CAC)

Adenoma detection studies											
Author, year	**Design**	**Primary outcome**	**Population**	***N***	**Adenoma detection (per-patient) CC**	**CAC**	***P***	**Adenoma detection (per-polyp) CC**	**CAC**	***P***	**Comments**
Hewett *et al.*, 2010	Cross-over (tandem), randomized order*	Adenoma miss-rate	High-risk (referral: surveillance/ screening)	100	69%	65%	N/A	1.85**	1.60**	N/A	- Adenoma miss-rate was significantly lower for CAC compared to CC (21% versus 33%; p=0.039) - Remarkably high adenoma detection rates
Wijkerslooth *et al.*, 2011	Parallel, randomized	Adenoma detection	Average-risk (population-based screening)	1,380	29%	29%	0.96	0.50	0.52	0.83	N/A

** Tandem design; results of detected polyps derived from 1st colonoscopy; polyp miss-rate (primary outcome) is displayed in the "comments" column*
*** Not reported in the study; derived from results*
**** Randomized to three different arms. Only results from CC and CAC arm are displayed; polyp detection rate of the "short hood" arm is not displayed*
***** Study was performed in two parts; first part non-randomized design (data not displayed), second part tandem design with fixed order in patients with adenomas at initial colonoscopy; randomization in second part after 1st (conventional) colonoscopy to either conventional colonoscopy or colonoscopy with retractable extension device.*
****** Randomized to four different arms. Only results from CC and CAC arm are displayed; results from two autofluorescence imaging (AFI) arms are not displayed. "Neoplasm" was defined as an adenoma (low or high grade), non-invasive carcinoma, invasive carcinoma or carcinoid*
- Horiuchi et al. 2009 not displayed: tandem design with fixed order; randomization after 1st (conventional) colonoscopy to either narrow-band imaging colonoscopy or colonoscopy with retractable extension device; due to design (absence of CC group) data extraction not possible

Table 4: Polyp and adenoma detection rates (per-patient and per-polyp analysis) in RCTs (CC versus CAC)

Polyp detection studies (or other primary outcome)											
Author, year	**Design**	**Primary outcome**	**Population**	***N***	**Polyp detection (per-patient) CC**	**CAC**	***P***	**Polyp detection (per-polyp) CC**	**CAC**	***P***	**Comments**
Tada *et al.*, 1997	Parallel, randomized	Cecal intubation time	High-risk (referral: FOBT+/ surveillance	140	N/A	N/A	N/A	0.58	0.86	< 0.05	- Histopathology not reported (only "lesions")
Matsushita *et al.*, 1998	Cross-over (tandem), randomized order*	Polyp detection rate	High-risk (referral: polyps at previous barium-enema)	24	N/A	N/A	N/A	3.33**	3.67**	N/A	- Polyp miss-rate was significantly lower for CAC compared to CC (15% versus 0%; p=0.0125) - Small polyps in recto-sigmoid were not removed
Kondo *et al.*, 2007* **	Parallel, randomized	Cecal intubation rate	High-risk (referral)	456	39.1%	49.3%	0.04	2.07**	2.05**	N/A	- Histopathology not reported
Horiuchi *et al., 2008* ** **	Tandem; fixed order; Parallel randomization after 1st colonoscopy	Cecal intubation time; number of adenomas	Patients with adenomas at 1st colonoscopy	60	N/A	N/A	N/A	1.50**	1.63**	N/A	- Compared to initial CC, CAC detected 10 additional adenomas compared to 2 additional adenomas in the CC group (p=0.029),

** Tandem design; results of detected polyps derived from 1st colonoscopy; polyp miss-rate (primary outcome) is displayed in the "comments" column*
*** Not reported in the study; derived from results*
**** Randomized to three different arms. Only results from CC and CAC arm are displayed; polyp detection rate of the "short hood" arm is not displayed*
***** Study was performed in two parts; first part non-randomized design (data not displayed), second part tandem design with fixed order in patients with adenomas at initial colonoscopy; randomization in second part after 1st (conventional) colonoscopy to either conventional colonoscopy or colonoscopy with retractable extension device.*
****** Randomized to four different arms. Only results from CC and CAC arm are displayed; results from two autofluorescence imaging (AFI) arms are not displayed. "Neoplasm" was defined as an adenoma (low or high grade), non-invasive carcinoma, invasive carcinoma or carcinoid*
- Horiuchi et al. 2009 not displayed: tandem design with fixed order; randomization after 1st (conventional) colonoscopy to either narrow-band imaging colonoscopy or colonoscopy with retractable extension device; due to design (absence of CC group) data extraction not possible

Table 4: Polyp and adenoma detection rates (per-patient and per-polyp analysis) in RCTs (CC versus CAC)

Lee *et al.* *2009*	Parallel, randomized	Cecal intubation rate	High-risk (referral: symptoms/ surveillance	1,000	37.5%	30.5%	0.018	0.96	0.63	0.023	- Shorter withdrawal time in the CAC group correlated with lower polyp detection rate - "Adenomas" are reported but included hyperplastic polyps
Harada *et al.*, 2009	Parallel, randomized	Cecal intubation time	High-risk (referral: symptoms/ surveillance/ screening)	592	42.4%	43.0%	0.88	1.50**	1.49**	N/A	- Not powered for polyp detection - Histopathology not reported
Takeuchi *et al.* 2010***	Parallel, randomized	"Neoplasm" detection rate	High-risk (referral: FOBT+/ surveillance)	274	55.6%	59.6%	N/A	1.19	1.72	0.21	- Results are displayed of detected "neoplasms"; 388 of 400 detected neoplasms were adenomas.
Tee *et al.*, 2010	Parallel, randomized	Cecal intubation time	High-risk (referral: symptoms/ surveillance/ screening)	400	31.3%	32.8%	0.75	0.74**	0.54**	N/A	- Not powered for polyp detection - Total number of adenomas was reported, but not the total number of patients with adenomas

** Tandem design; results of detected polyps derived from 1st colonoscopy; polyp miss-rate (primary outcome) is displayed in the "comments" column*
*** Not reported in the study; derived from results*
**** Randomized to three different arms. Only results from CC and CAC arm are displayed; polyp detection rate of the "short hood" arm is not displayed*
***** Study was performed in two parts; first part non-randomized design (data not displayed), second part tandem design with fixed order in patients with adenomas at initial colonoscopy; randomization in second part after 1st (conventional) colonoscopy to either conventional colonoscopy or colonoscopy with retractable extension device.*
****** Randomized to four different arms. Only results from CC and CAC arm are displayed; results from two autofluorescence imaging (AFI) arms are not displayed. "Neoplasm" was defined as an adenoma (low or high grade), non-invasive carcinoma, invasive carcinoma or carcinoid*
- Horiuchi et al. 2009 not displayed: tandem design with fixed order; randomization after 1st (conventional) colonoscopy to either narrow-band imaging colonoscopy or colonoscopy with retractable extension device; due to design (absence of CC group) data extraction not possible

Table 4: Polyp and adenoma detection rates (per-patient and per-polyp analysis) in RCTs (CC versus CAC)

Dai *et al.*, 2010	Parallel, randomized	Not specified	High-risk (referral)	250	14.7%**	15.7%**	N/A	0.24**	0.27**	N/A	- Not powered for polyp detection - Histopathology not reported
Park *et al.*, 2011	Tandem; fixed order; Parallel randomization after 1st colonoscopy	Cecal intubation time; polyp miss rate	Patients being referred for removal of unresectable polyps	329	N/A	N/A	N/A	3.4	2.7	0.003	- Compared to initial CC, number of detected polyps was significantly higher in CAC compared to CC (1.65 versus 0.86; p=0.026),

** Tandem design; results of detected polyps derived from 1st colonoscopy; polyp miss-rate (primary outcome) is displayed in the "comments" column*
*** Not reported in the study; derived from results*
**** Randomized to three different arms. Only results from CC and CAC arm are displayed; polyp detection rate of the "short hood" arm is not displayed*
***** Study was performed in two parts; first part non-randomized design (data not displayed), second part tandem design with fixed order in patients with adenomas at initial colonoscopy; randomization in second part after 1st (conventional) colonoscopy to either conventional colonoscopy or colonoscopy with retractable extension device.*
****** Randomized to four different arms. Only results from CC and CAC arm are displayed; results from two autofluorescence imaging (AFI) arms are not displayed. "Neoplasm" was defined as an adenoma (low or high grade), non-invasive carcinoma, invasive carcinoma or carcinoid*
- Horiuchi et al. 2009 not displayed: tandem design with fixed order; randomization after 1st (conventional) colonoscopy to either narrow-band imaging colonoscopy or colonoscopy with retractable extension device; due to design (absence of CC group) data extraction not possible

our control group did minimize the risk of investigator bias and did secure a solid comparison to cap-assisted colonoscopy.

In our study, adenoma detection rates in the cap-assisted colonoscopy group were comparable to those in the conventional colonoscopy group and varied from 24% to 35%. Only one endoscopist, who performed 54 colonoscopies in this study, detected significantly more patients with at least one adenoma in the CC group than in the CAC group (55% versus 24%; p=0.02), but this difference did not affect the overall results. In the literature, mixed results have been reported on improvement of polyp detection by CAC **(Table 4)**.(3-11) The majority of these studies did not report histopathology of detected polyps. One Japanese study with a similar design reported a higher polyp detection in the CAC group.(4) In contrast, a Chinese study reported lower polyp detection rates in CAC, but polyp detection was also correlated with withdrawal time.(3) Two other parallel randomized controlled trials reported similar polyp detection rates, but these studies did not achieve enough power to compare polyp detection.(5;8) A limited number of CAC studies did report histopathology. Two tandem studies showed improvement of adenoma detection by CAC.(9;10) However adenoma miss-rates in the control groups were lower than expected based on miss-rates in a meta-analysis, suggesting investigator bias.(1) Hewett and Rex studied CAC in a Western population and found that CAC decreased adenoma miss-rates, especially for small size adenoma miss-rates.(11) In this study, adenoma detection rates of the participating endoscopists were remarkably high (69% for CC versus 65% for CAC), making these results less applicable to daily clinical practice. Although a tandem design, as used in this study, is generally considered the most reliable, it can lead to investigator bias in studies in which blinding for the technique is impossible. In our study, a large number of conventional and cap-assisted colonoscopies were consecutively performed in a random order, through which we aimed to mimic daily clinical practice.

Cecal intubation times of the CAC group were reduced by more than one minute in our study, which is in accordance with findings from other CAC studies.(3-5) This reduction may be caused by the protruding cap, which may facilitate sliding along folds and flexures allowing quick advancement of the colonocope to the cecum. Furthermore, CAC may be especially helpful in patients with difficult bowel anatomy, such as female patients, old patients, patients with previous abdominal surgery and patients with left-sided diverticulosis.(4) However, the cecal intubation rates were not improved by CAC and were equal to those in other studies in the literature.(3;5)

We showed that participants undergoing CAC had lower discomfort scores during colonoscopy. This finding is in accordance with the literature.(5;24;25) However, after two weeks, no significant differences in the perceived burden of the procedure were reported. Discomfort during colonoscopy was scored by the research staff, whereas

the burden after two weeks was reported by subjects themselves. Investigator bias may be an explanation for these conflicting results. A subanalysis in women demonstrated lower pain scores two weeks after colonoscopy for cecal intubation and withdrawal of the colonoscope, a finding that is in line with the literature.(5)

We compared the adenoma detection between CAC and CC in experienced endoscopists. It has previously been reported that CAC improved cecal intubation rates in female patients among trainee endoscopists.(4) CAC may be a useful method in the improvement of adenoma detection by less experienced endoscopists, but further studies are needed to confirm this. A possible disadvantage of CAC is the visibility of the cap on the monitor during colonoscopy reducing the visual field. A possibility for improving this could be the development of a cap with an angle that is similar to the field of view of the colonoscope (140° or 170°). In this case, the cap can smooth colonic folds without blurring the endoscopic view. In addition, because of the oblique sides, the chance of fecal residue remaining in the cap may be lower and maneuvering the cap to each fold may take less effort due to the extended range of the cap. Another option is to combine CAC with other advanced imaging techniques. A Japanese study combined CAC and autofluorescence imaging (AFI) and found higher "neoplasm detection rates" (adenomas, carcinomas and carcinoids altogether) compared to white light endoscopy only (1.96 versus 1.19; p=0.02).(7) The conclusion that a combination of these techniques improves adenoma detection seems premature. Further studies are needed to verify these results. A recent study showed that CAC improved polyp detection in patients referred for endoscopic mucosal resection of polyps detected during an initial CC that could not be removed with standard biopsy forceps.(26) CAC may possibly have a role during a "second look" in patients being referred for removal of (large) colorectal polyps.

We conclude from this large randomized controlled trial that CAC does not improve adenoma detection. It does reduce cecal intubation times and is safe, as no complications occurred. On the basis of the results of our study, we strongly feel that CAC should not be used in daily clinical practice to improve the detection of adenomas. It may be useful in reducing cecal intubation time and patient discomfort. This technique could therefore be used for these indications

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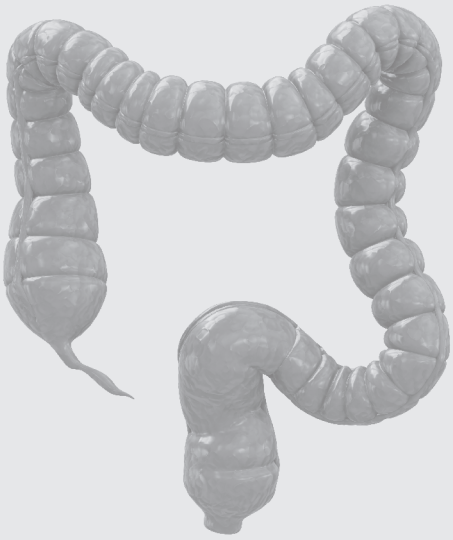
CHAPTER 9

Summary and General discussion



E. M. Stoop

SUMMARY AND GENERAL DISCUSSION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females. About 608,000 deaths from colorectal cancer are estimated worldwide, accounting for 8% of all cancer deaths, making it the fourth most common cause of death from cancer. (2) The prognosis of CRC depends on the stage at the time of diagnosis; in the Netherlands, the 5-year-survival rate of stage I CRC is 94% compared to 8% for stage IV.(4) In most cases, CRC develops from adenomatous polyps after a long premalignant state. Early detection and removal of these precursor lesions reduce both the incidence and mortality of CRC. (88) Therefore, screening is needed to bring forward the time of diagnosis during this premalignant state or curable state.

Screening programs for colorectal cancer (CRC) are being implemented in most Western countries. The European Union (EU) recommends population-based screening for colorectal cancer using evidence-based tests with quality assurance of the entire screening process including diagnosis and management of patients with screen-detected lesions. (89) In 2009, 19 out of 27 European countries had established or were preparing a population-based or opportunistic CRC screening program. (66) Although screening for colorectal cancer is gaining acceptance throughout the world, there is no single preferred screening strategy.

Colonoscopy is considered the reference standard for detection of adenomas and CRC. Tandem-colonoscopy studies showed that the sensitivity of colonoscopy varies between 90%-98% for detection of large adenomas (>10mm) and around 87% for 6-9mm adenomas.(23) Disadvantages are the need for full bowel cleansing, burden of the procedure, and the complication rate of 0.1% to 0.3%, including post-polypectomy bleeding and perforation. (25, 26)

CT-colonography is another structural exam to visualise the complete colon. Its estimated sensitivity in detecting adenomas $\geq$10mm in a screening population is 88%, versus 79% for 6 to 9mm adenomas.(27) Disadvantages are the exposure to ionizing radiation, although low dose protocols are now available. Besides, there is the need for subsequent colonoscopy if significant lesions are detected.

This thesis aimed to compare the efficacy, accuracy and applicability of colonoscopy and CT-colonography in a population-based screening program for colorectal cancer (CRC) (chapter 2). Besides, burden of both screening methods (chapter 3), costs of colonoscopy screening (chapter 4), two strategies for pre-colonoscopy assessment (chapter 5), sensitivity and specificity of fecal immunochemical testing (FIT) (chapter 6), detection of proximal serrated polyps (chapter 7) and the surplus value of cap-assisted colonoscopy (chapter 8) were studied and evaluated.

For these purposes, individuals aged 50-75 years of the general Dutch population were randomized to either colonoscopy or CT colonography for primary CRC screening.

In **chapter 2** of this thesis, participation rates and diagnostic yield of the two screening methods were studied. A total of 8,844 persons were randomly allocated to colonoscopy (n=5,924) or non-cathartic CT-colonography (n=2,920) screening. The participation rate was significantly higher in the CT colonography arm than in the colonoscopy arm; a total of 1,276 (22%) colonoscopy invitees attended colonoscopy versus 982 (34%) CT colonography invitees attending CT Colonography (p= <0.0001).

On the other hand, colonoscopy identified 43% more advanced neoplasia in participants than CT-colonography (8.7% versus 6.1%, p=0.02). These two significant differences more or less levelled each other out in the diagnostic yield per invitee, which was similar in both groups: 1.9 per 100 invitees were identified with at least one advanced neoplasia in the colonoscopy group versus 2.1 per 100 in the CT-colonography group (p=0.56). These results led to the conclusions that CT-colonography screening is associated with higher participation, colonoscopy with higher diagnostic yield in participants, and that both methods have a similar diagnostic yield in detecting advanced neoplasia on the invitee level.

These results were based on first-round screening of a screening-naïve population. Further surveillance is likely to increase the yield of advanced lesions. In our protocol, screenees who were diagnosed by CT-colonography with a 6-9 polyp without accompanying larger lesions were scheduled to undergo surveillance CTC at 3 years. Screenees who were diagnosed with advanced neoplasia during colonoscopy also will need to undergo surveillance within 1-3 years according to the guidelines. Both 1st and later round surveillance are expected in both groups to increase the yield of advanced lesions over time, but these results were beyond the time-frame of the study described in Chapter 2.

In the Netherlands, several CRC screening trials have been conducted in the last few years[15, 16, 90]. The Dutch participation rates of gFBOT and FIT screening (47% to 50% and 60% to 62%, respectively) were higher than the participation rates of colonoscopy and CT-colonography that were found in this trial (15, 16). Sigmoidoscopy screening had a participation rate of 32% in the Netherlands (15), which was comparable to CT-colonography screening. Participation rates of all screening techniques could be increased by increasing public-awareness through large campaigns, or by more actively involving general practitioners in the invitation process. Although both gFOBT and FIT had higher participation rate compared to the other available screening techniques, the diagnostic yield of 0.6 and 1.4 to 1.5 per 100 invitees, respectively, were lower than with colonoscopy and CT-colonography screening (chapter 2).

To determine which screening technique is preferable in a population-based screening program for CRC, other factors, like burden of the procedure have to be taken into account. Initial participation can be influenced by the expected burden of the screening test. Those who anticipate the screening procedure to be burdensome may be less likely to take part. The actually perceived burden of the procedure could play a role in future program adherence.

In previous studies CT-colonography was found to be superior in terms of overall patient preferences.(91, 92) However, these studies were non-randomized and used a tandem design, in which CT-colonography was performed prior to colonoscopy. This gives participants the opportunity to compare the perceived burden of both techniques, but suffers from having a fixed sequential order. To our knowledge no studies have been published comparing both the expected and perceived burden of colonoscopy and CT-colonography.

In **chapter 3** of this thesis, expected and perceived burden were studied and compared for the two screening methods. All invitees twice received a validated questionnaire on the burden of the screening procedure (EBQ); one within 4 weeks before the screening procedure focusing on the expected burden, and a second questionnaire 14 days after the examination on the perceived burden (PBQ). With the EBQ we collected information on the expected embarrassment, pain and burden of the bowel preparation and the examination itself. The PBQ contained items on perceived embarrassment, pain and burden of the bowel preparation, the examination itself and the overall burden of the screening procedure. Mean scores were calculated on 5-point scales. This showed that colonoscopy invitees expected the screening procedure and bowel preparation to be more burdensome than CT colonography invitees. However, significantly more participants perceived the CT-colonography as more burdensome than colonoscopy. Colonoscopy participants rated the entire screening procedure more often as not or only slightly embarrassing (95% versus 92%, $p<0.001$), more often as not painful (53% versus 28%; $p<0.001$) and more often as not burdensome (48% versus 34%, $p<0.001$). Nevertheless, the level of intended participation in a next screening round was comparable in both groups.

Another important factor in making a decision which screening technique is achievable in population wide screening are the costs for such a screening method. A number of economic analyses have been performed to estimate the cost-effectiveness of primary colonoscopy screening.(38-40) In these analyses colonoscopy costs were generally based on clinical reimbursements, based on routine patient care. These estimates may not be representative of the actual costs for screening colonoscopies. Screening costs were most likely overestimated, presuming that costs for one colonoscopy in a dedicated high throughput screening setting are lower than the costs for a regular colonoscopy in a clinical setting. Analyses estimating the true unit costs

in a population-based screening program, using colonoscopy as a primary screening method are lacking.

In **chapter 4** of this thesis, the real unit costs per colonoscopy in a dedicated screening setting were studied. Costs were calculated for the invitational process, a pre-colonoscopy assessment, the colonoscopy itself, the assessment of histopathology and report of final test results by a general practitioner. In this dedicated screening setting, sixteen colonoscopies were performed per 8-hour workday. The total costs including all materials and personnel costs per screening colonoscopy amounted to €252.30. Several possible scenarios in colonoscopy screening were described, such as; screening performed by endoscopy nurses instead of a gastroenterologist (€206.31), extended screening during evening hours (€252.41), and colonoscopy screening without the use of sedatives (€239.79). The average costs per colonoscopy in a dedicated screening setting are considerably less than current reimbursement rates for clinical colonoscopy.

Since many economic evaluations have relied on reimbursement rates as a proxy for the unit costs of a screening colonoscopy, the actual costs per life-year saved through CRC screening with primary colonoscopy may be lower than estimated in these evaluations, resulting in improvement of the cost-effectiveness of CRC screening with primary colonoscopy.

When colonoscopy is used as a primary screening method, the risks and benefits of screening therefore have to be explained to participants before screening to enable informed decision-making. Besides, information on a person's medical history and medication use should be obtained to anticipate on possible risks during colonoscopy. On one hand screenees need to be adequately informed on the risks and benefits of the procedure, and on the other hand the endoscopist and screening organization require adequate information on the health status of the individual screenee and the need for any specific precautions. Both aims can be achieved in a pre-colonoscopy consultation.

In an RCT within the large COCOS trial, invitees were randomized (prior to invitation) into either a pre-colonoscopy consultation by telephone prior to colonoscopy (n=3,302) or a pre-colonoscopy assessment at the outpatient clinic (face-to-face) (n=3,298). This study was described in **chapter 5** of this thesis. The study aimed to compare the response rate and participation rate between both groups. Secondary outcomes were participants' satisfaction, expected and perceived burden, and quality of bowel preparation. (93). Response rates to the pre-colonoscopy assessment were similar in both groups, but colonoscopy attendance was significantly lower in the telephone group (20% versus 23%, p=0.018). Significantly more persons did not attend colonoscopy after the pre-colonoscopy assessment by telephone. Invitees and responders in the telephone group expected the bowel preparation to be more

painful than those in the face-to-face group. On the other hand, significantly more subjects in the face-to-face group than in the telephone group were satisfied by the consultation in general (99.8% versus 98.5%; p= 0.014). Quality of bowel preparation turned out to be similar in both groups.

In a population-based screening program using colonoscopy as the primary screening method, it is thinkable that an intake at the outpatient clinic for all screenees might overload the outpatient clinic. Therefore, further research should focus on how to raise colonoscopy participation rate after a telephone consultation. Based on our results, we do not recommend switching to a pre-colonoscopy assessment by telephone because of the lower post-consultation uptake of colonoscopy.

Fecal immunochemical testing (FIT) is increasingly used for colorectal cancer (CRC) screening. Although FIT-screening is implemented worldwide, solid data evaluating FIT against colonoscopy as the reference standard are scarce as most studies to date have only performed colonoscopy in subjects with a positive FIT, but not in those with a negative FIT, so reliable data about sensitivity and specificity are lacking. Other studies comparing FIT and colonoscopy included participants of non-invitational screening programs. In such programs, the proportion of participants with a positive CRC family history was higher compared with our study (13–14 vs. 3%).(36, 37)

To our knowledge, this is the first study evaluating the accuracy of FIT within an invitational population-based colonoscopy screening program.

Therefore, in **chapter 6** of this thesis, we aimed to estimate the sensitivity, specificity and predictive values of FIT in a screening population measured against colonoscopy (for cut-off levels of 50(FIT50), 75(FIT75) and 100(FIT100) ng Hb/ml) In addition, we aimed to evaluate FIT sensitivity in detecting right-sided and left-sided neoplasia. In order to do this, all screening participants who were willing to undergo colonoscopy were asked to complete one sample FIT (OC-Sensor) prior to their screening colonoscopy. Almost nine out of 10 screenees with CRC, three to four out of 10 with advanced adenoma, and four out of 10 with advanced neoplasia were detected using a single FIT at a low cut-off of 50 ng/ml. For FIT75, sensitivity and specificity for advanced neoplasia were 33% and 96% respectively and for FIT100 these numbers were 31% and 97% respectively. Sensitivity of FIT 50 for CRC was 88% and specificity was 91%. Sensitivity and specificity of FIT 75 for CRC were 75% and 93% respectively and FIT100 had a sensitivity of 75% en specificity of 95%. Besides, sensitivity for proximal and distal neoplasia turned out to be similar.

We showed that FIT has a high sensitivity in the detection of CRC and a moderate sensitivity in detecting advanced neoplasia within an invitational colonoscopy screening program. In contrast to previous findings, (94, 95), the sensitivity of FIT in detecting proximal and distal advanced neoplasia was equal. Adding a second FIT sample can increase the positivity rate of FIT.(90) When FIT is repeated every two years, sensitivity

of FIT might be comparable to the sensitivity of colonoscopy, performed once in ten years. Lowering the cutoff level or raising the number of tests will result in a higher sensitivity but lower specificity of FIT. Further studies, including cost-effectiveness studies need to be done to find the optimal interval for repeat FIT screening.

Although colonoscopy is considered the most accurate method and reference standard for the detection of colorectal neoplasia, it can still miss a substantial number of polyps. This seems especially the case for right-sided polyps. The prevalence of left-sided advanced colorectal advanced neoplasia, but not right-sided advanced neoplasms, was strongly reduced within a ten-year period after colonoscopy in a German trial. (43) A Canadian study demonstrated a marked difference in the strength of the association of colonoscopy with CRC death for proximally and distally located cancers. (44) One of the reasons may be that proximal adenomas are often flat and more difficult to identify than pedunculated and sessile polyps that predominate in the left colon. (45) In addition, distal cancers are more likely to develop through the chromosomal instability pathway with the classic slow progression of adenoma to carcinoma than proximal colon cancers. (45) This might be an explanation for the difference in colonoscopic detection of polyps between de left and right colon.

Proximally located serrated polyps also have a flat morphology and ambiguous color. In combination with insufficient bowel preparation of the proximal colon, there is an increased risk of not detecting these lesions during colonoscopy. These serrated polyps can develop into CRC through the serrated pathway.(93, 96) Besides, previous studies have demonstrated an association between proximal location of serrated polyps with synchronous advanced neoplasia and CRC, implying a higher risk of advanced neoplasia during surveillance. (97, 98) This implies that these proximally located polyps are an important issue in colonoscopy screening.

In **chapter 7** of this thesis, we performed a prospective study within our randomized controlled trial, to identify patient-related and procedure-related factors associated with the detection of proximal serrated polyps (PSP). The rate of detection of PSP significantly differed between experienced endoscopists. No significant effects of age, gender or quality of the bowel preparation were observed.

In contrast, withdrawal time was strongly and significantly associated with proximal serrated polyp detection. Endoscopists with lower PSP detection rates should be encouraged to detect and remove all polyps. For these endoscopists, increasing awareness of the risk of PSP may be necessary and additional training to improve SP detection could be beneficial. A longer withdrawal time could also improve detection of these serrated lesions.

Recent studies demonstrated that patients with large PSPs are at increased risk of synchronous and likely metachronous advanced neoplasia and colorectal cancer.

(97-99) Next to adenoma detection rates, PSP detection rates should be as high as possible. For endoscopists, awareness of the risk of PSP must be increased.

Improved bowel preparation, more advanced and flexible colonoscopes and training of endoscopists, may all lead to improved adenoma detection. Another improvement in adenoma detection could be cap-assisted colonoscopy, because colonoscopy combined with a transparent plastic cap may improve colonic visualization.

In **chapter 8** of this thesis, we described our study comparing adenoma detection of conventional colonoscopy with cap-assisted colonoscopy. Secondary outcomes in this study were cecal intubation time, cecal intubation rate and the degree of discomfort during colonoscopy. Final result was that cap- assisted colonoscopy did not improve adenoma detection, but it did reduce cecal intubation time by more than 1 min. Besides, it lowered the degree of discomfort during colonoscopy.

The lowered degree of discomfort is in accordance with the literature,(100, 101) as is the shorter intubation time.(100, 102, 103) Based on our results, we conclude that CAC should not be used in daily clinical practice. It may be useful in specific patients such as female patients, patients with previous abdominal surgery or patients with left-sided diverticulosis to reduce discomfort and cecal intubation time.

CONCLUSION

Our results provide an answer to the important question whether colonoscopy or CT colonography is a more efficient, accurate and eligible screening method in a population-based screening program for colorectal cancer. It turns out that colonoscopy, albeit associated with lower uptake has a higher diagnostic yield per participant in detecting advanced neoplasia. This results in a similar advanced neoplasia detection rate per invitee. This is for colonoscopy in this study achieved at a lower screenee burden than CT-colonography. Future studies on the role of colonoscopy should focus on maintenance of the current high uptake levels of colonoscopy after a positive FIT, on increasing the uptake of colonoscopy for those who require primary screening and/or surveillance with this invasive method, and on cost-efficacy of colonoscopy screening.

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NEDERLANDSE SAMENVATTING

Dit proefschrift had allereerst tot doel om de accuratesse, betrouwbaarheid en toepasbaarheid van coloscopie en CT colografie met elkaar te vergelijken als primaire screenings-methoden in een bevolkingsonderzoek naar colorectaal carcinoom (CRC) (hoofdstuk 2). Daarnaast werd de belasting voor de deelnemer van de twee screeningsmethoden vergeleken (hoofdstuk 3). In hoofdstuk 4 werden de kosten van coloscopie screening berekend en in hoofdstuk 5 werden twee verschillende inclusiemethoden voorafgaande aan de coloscopie met elkaar vergeleken. De sensitiviteit en specificiteit van een ontlastingtest op occult bloed (FIT) werd onderzocht in hoofdstuk 6 en de mate van detectie van serrated poliepen, proximaal in het colon in hoofdstuk 7. Tenslotte werd in hoofdstuk 8 de toegevoegde waarde van colonoscopie met plastic cap besproken.

Om deze studies te kunnen uitvoeren werden personen tussen de 50 en 75 jaar oud gerandomiseerd voor coloscopie of CT colografie in het kader van primaire CRC screening.

In **hoofdstuk 2** van dit proefschrift werden ten eerste beide screeningsmethoden vergeleken met betrekking tot de deelname graad en de diagnostische opbrengst ten aanzien van advanced neoplasie. Advanced neoplasie werd daarbij conform internationale standaarden gedefinieerd als een advanced adenoom of colorectaal carcinoom. In totaal werden 8.844 personen gerandomiseerd voor coloscopie (n=5,924) of CT colografie (n=2,920) screening. De deelname graad was significant hoger in de CT colografie arm dan in de coloscopie arm; 1,276 (22%) van de coloscopie deelnemers ondergingen een coloscopie ten opzichte van 982 (34%) van de CT colografie deelnemers die een CT colografie ondergingen. De diagnostische opbrengst onder deelnemers was echter significant hoger in de coloscopie arm. Bij coloscopie werd 1.43 keer meer advanced laesies gevonden dan in de CT colografie groep (8.7% versus 6.1%). Deze significant hogere deelname in de CT colografie groep maar anderzijds de significant hogere diagnostische opbrengst per deelnemer in de coloscopie groep resulteren in een vrijwel gelijke diagnostische opbrengst per uitgenodigde. In de coloscopie groep had 1.9 per 100 uitgenodigden een advanced neoplasie ten opzichte van 2.1 per 100 uitgenodigden in de CT colografie groep.

Om te kunnen beslissen welke screeningsmethode de voorkeur heeft in een bevolkingsonderzoek naar CRC moeten echter ook andere factoren, zoals belasting van de patiënt worden meegenomen.

In **hoofdstuk 3** van dit proefschrift werden de verwachtte en de ervaren belasting van coloscopie en CT colografie onderzocht. Alle uitgenodigde personen ontvingen twee maal een gevalideerde vragenlijst met vragen over de verwachtte en ervaren belasting van het onderzoek waar zij voor gerandomiseerd waren. Vier weken voor

het onderzoek ontvingen zij een vragenlijst gericht op de verwachtte belasting (Expected Burden Questionnaire - EBQ), en twee weken na het onderzoek een vragenlijst gericht op de ervaren belasting (Perceived Burden Questionnaire - PBQ). Met behulp van de EBQ werd informatie verzameld over de verwachtte schaamte, pijn en belasting ten aanzien van de darmvoorbereiding en het onderzoek zelf. Met behulp van de PBQ werd informatie verkregen aangaande de ervaren schaamte, pijn en belasting van de darmvoorbereiding en het onderzoek zelf. Tevens werd informatieverkregen over de ervaren belasting ten aanzien van het gehele screeningsproces. Gemiddelde scores werden weergegeven op 5-punts schalen.

Het resultaat was dat uitgenodigde personen voor coloscopie een hogere belasting verwachtten dan de uitgenodigde personen voor CT colografie. De ervaren belasting ten aanzien van het gehele screeningsproces bleek echter significant hoger in de CT colografie groep dan in de colonoscopie groep.

De verwachtte deelname in een volgende screeningsronde was gelijk in beide groepen.

In **hoofdstuk 4** van dit proefschrift werden de kosten per coloscopie in een speciaal ingerichtte screening setting berekend. De kosten werden apart berekend voor het uitnodigingsproces, het intake gesprek voorafgaande aan de coloscopie, de coloscopie zelf, histologische beoordeling door een patholoog anatoom en het rapporteren van de testuitslagen door de huisarts.

In onze speciaal voor screening ingerichtte setting konden 16 coloscopieën worden verricht op een 8-urige werkdag. De totale kosten voor een coloscopie in deze setting waren €252.30. Tevens werden er verschillende scenario's beschreven die mogelijk zouden kunnen zijn in primaire coloscopie screening. Een mogelijk scenario betrof screenings-coloscopie door endoscopie verpleegkundigen in plaats van een MDL arts. Hierdoor zou de prijs per coloscopie dalen naar €206.31. Andere mogelijk scenario's betroffen coloscopie screening gedurende dag- en avonduren (€252.41), en coloscopie screening zonder het gebruik van midazolam (€239.79). De berekende kosten voor een screenings coloscopie in een speciaal ingerichtte screening setting zijn beduidend lager dan de reguliere DBC prijs.

Voorafgaande aan een coloscopie is een intakegesprek nodig om deelnemers te informeren over het onderzoek en om de algehele gezondheid en mogelijke risicofactoren of contraindicaties te bespreken. Om twee verschillende uitvoeringen van een intakegesprek te vergelijken, werden personen voordat zij werden uitgenodigd, gerandomiseerd voor een telefonische intake (n=3,302) of een intake of een poliklinische intake (n=3,298). Deze studie werd beschreven in **hoofdstuk 5** van dit proefschrift. Het doel van deze studie was om de opkomst op het intakegesprek en vervolgens de daadwerkelijke deelname aan de coloscopie te vergelijken tussen beide groepen. Secundaire uitkomsten van deze studie waren tevredenheid van de deelne-

mer, de verwachtte en ervaren belasting van het onderzoek en de kwaliteit van de darmvoorbereiding. De deelname graad aan het intakegesprek was in beide groepen gelijk. Echter, de deelname aan de coloscopie was significant hoger in de groep met een poliklinische intake. Er waren significant meer personen in de telefonische arm dan in de poliklinische arm die geen coloscopie ondergingen. Uitgenodigde personen voor en deelnemers aan het telefonische intake gesprek verwachtten meer pijn te hebben tijdens de darmvoorbereiding dan de uitgenodigde personen en deelnemers in de poliklinische groep. Significant meer deelnemers in de poliklinische groep dan in de telefonische groep waren tevreden met het intake gesprek (99.8% versus 98.5%; p=0.016) De kwaliteit van de darmvoorbereiding was gelijk in beide groepen.

De immunochemische feces occult bloed test (FIT) wordt in toenemende mate gebruikt in CRC screening. Hoewel screening met behulp van FIT wereldwijd wordt toegepast zijn er weinig studies gedaan waarbij de sensitiviteit van FIT is onderzocht door te vergelijken met coloscopie als gouden standaard. In de meeste studies wordt enkel een coloscopie verricht na een positieve FIT maar niet na een negatieve FIT.

In **hoofdstuk 6** van dit proefschrift werden de sensitiviteit, de specificiteit en de positief en negatief voorspellende waarde van FIT bekeken bij gebruik van verschillende afkapwaarden respectievelijk 50 (FIT50), 75 (FIT75) en 100 (FIT100) ng Hb/ml). Daarnaast bekeken we de sensitiviteit van FIT ten aanzien van rechtszijdige en linkszijdige neoplasie. Om dit te bereiken werden alle deelnemers aan de coloscopiescreening gevraagd om een eenmalige FIT (OC-Sensor) af te nemen voorafgaande aan de coloscopie. Negen van de tien deelnemers met een colorectaal carcinoom, 3 tot 4 van de 10 met een advanced adenoom en 4 van de 10 met advanced neoplasie werden geidentificeerd met een eenmalige FIT met afkapwaarde 50 ng/ml. De sensitiviteit en specificiteit voor advanced neoplasie van de FIT75 waren respectivelijk 33% en 96%. De FIT100 had een sensitiviteit van 31% en een specificiteit van 97%. De sensitiviteit van FIT voor proximale en distale neoplasie bleek gelijk.

Ondanks het feit dat coloscopie wordt gezien als de meest accurate methode en de gouden standaard voor de detectie van colorectale neoplasie, kunnen er toch adenomen worden gemist. Dit lijkt met name het geval te zijn bij poliepen gelokaliseerd in het rechter colon. Een van de redenen voor dit verschil zou kunnen zijn dat proximaal gelokaliseerde adenomen vaak vlakker zijn dan distaal gelokaliseerde adenomen. Daarnaast ontwikkelen distaal gelokaliseerde adenomen zich vaker via de chromosomal instability pathway tot een colorectaal carcinoom dan proximaal gelokaliseerde adenomen. Hierbij vindt er een langzame progressie plaats van adenoom tot carcinoom. Dit zou een van de verklaringen kunnen zijn voor het verschil in detectie-graad van neoplasie tussen het linker- en rechter colon.

Proximaal gelokaliseerde serrated poliepen hebben een vlakke morfologie en een onopvallende kleur. In combinatie met de soms matige kwaliteit van de darmvoorbe-

reiding van het proximale colon kunnen deze adenomen dus ook makkelijk gemist worden. Deze serrated adenomen kunnen ontaarden in colorectaal carcinoom via de serrated pathway. Eerdere studies hebben aangetoond dat er een relatie bestaat tussen proximaal gelokaliseerde serrated adenomen en synchrone advanced neoplasie en CRC. Dit impliceerd dat deze proximaal gelokaliseerde serrated adenomen een belangrijke plaats innnemen in coloscopie screening.

In **hoofdstuk 7** van dit proefschrift werd een prospectieve studie beschreven om patiëntgebonden en proceduregebonden factoren te identificeren welke geassocieerd zijn met detectie van deze proximaal gelokaliseerde serrated adenomen. De mate van detectie van deze proximaal serrated adenomen was significant verschillend tussen de ervaren endoscopisten. Er werd geen significant effect van leeftijd of geslacht van de deelnemer op de detectie van proximaal gelokaliseerde serrated adenomen vastgesteld en ook de kwaliteit van de darmvoorbereiding had geen invloed. De terugtrektijd tijdens de coloscopie was wel significant geassocieerd met proximaal gelokaliseerde serrated adenomen detectie.

Er wordt continu gezocht naar verbetering van endoscopische technieken. Verbeterde kwaliteit van de darmvoorbereiding, geavanceerdere coloscopen en training van endoscopisten kunnen allemaal leiden tot toegenomen adenomen detectie.

Een andere verbetering in detectie van advanced neoplasie zou een transparant plastic cap op de tip van de coloscoop kunnen zijn. Deze plastic cap zou de visualisatie van de mucosa van het colon kunnen verbeteren. In **hoofdstuk 8** van dit proefschrift werd de adenomen- detectie vergeleken tussen een conventionele coloscopie en een coloscopie met plastic cap (CAC). Secundaire uitkomsten in deze studie waren het aantal succesvolle coecum intubaties, de coecum intubatie tijd en de mate van discomfort tijdens de procedure. Het resultaat van de studie was dat een coloscopie met plastic cap, de adenomen detectie niet verbeterde. Wel nam de coecum intubatietijd af met meer dan 1 minuut, en tevens nam de belasting van de coloscopie af.

Om antwoord te geven op de vraag of coloscopie of CT colografie accurater, betrouwbaarder en beter toepasbaar is in darmkankerscreening, kunnen onze onderzoeksresultaten gebruikt worden. Hoewel de deelnamegraad bij coloscopie lager is dan bij CT colografie, is de diagnostische opbrengst ten aanzien van advanced neoplasie per deelnemer hoger bij coloscopie dan bij CT colografie. Dit resulteert in een gelijke diagnostische opbrengst van advanced neoplasie per uitgenodigde. Echter, de CT colografie werd als meer belastend ervaren door deelnemers dan de coloscopie. Ervaren belasting bepaald in grote mate de opkomst bij een volgende screeningsronde. Toekomstige studies naar darmkankerscreening met behulp van coloscopie moeten gericht worden op het behoud van de hoge deelnamegraad in coloscopiescreening na een positieve FIT en op verhogen van de deelnamegraad in

primaire coloscopiescreening en coloscopie surveillance. Daarnaast zal de kosten-effectiviteit van coloscopiescreening verder onderzocht moeten worden.

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PhD PORTFOLIO

Oral presentations

2011 Participation and Yield of Colonoscopy versus Non-Cathartic CT Colonography in Population-Based Colorectal Cancer Screening: a Randomized Controlled Trial.
Digestive Disease Week, Chicago, United States.

2009 Population Screening for Colorectal Cancer by Colonoscopy or CT Colonography: a Randomized ControlledTrial.
Dutch Society of Gastroenterology, Veldhoven, the Netherlands

Poster presentations

2011 The Colonoscopy Unit Costs of Population-based Screening for Colorectal Cancer.
Face-to-Face vs Telephone Pre-Colonoscopy Consultation in Colorectal Cancer Screening; a Randomized Trial.
Digestive Disease Week, Chicago, United States.

Attended seminars and workshops

2011 English Biomedical Writing and Communication
Erasmus University Medical Center, Rotterdam, the Netherlands

2009 Erasmus Summer Program:
Biostatistics for Clinicians
Principles in Research of Medicine
Netherlands Institute for Health Sciences (NIHES), Rotterdam, the Netherlands.

LIST OF PUBLICATIONS

Study protocol: population screening for colorectal cancer by colonoscopy or CT Colonography: a randomized controlled trial.
T.R. de Wijkerslooth, M.C. de Haan, E.M. Stoop, M. Deutekom, P. Fockens, P.M. Bossuyt, M. Thomeer, M. Van Ballegooijen, M.L. Essink-Bot, M.E. van Leerdam, E.J. Kuipers, E. Dekker, J. Stoker.
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Submitted

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CURRICULUM VITAE

Esther Maria Stoop werd geboren op 18 februari 1982 in Deventer. In 2000 behaalde zij haar Atheneum examen aan het Thomas a Kempis College te Arnhem. In 2001 begon zij aan de studie Geneeskunde te Rotterdam waarna zij in 2007 haar artsexamen behaalde. Zij werkte vervolgens anderhalf jaar als ANIOS op de afdeling Thoraxchirurgie. In april 2009 startte zij met promotieonderzoek op het gebied van dikke darmkankerscreening onder leiding van prof. dr. E. J. Kuipers en dr. M.E. van Leerdam. Naast haar promotieonderzoek werkte zij nacht- en weekenddiensten als poortarts op de Spoedeisende Hulp van het Jeroen Bosch Ziekenhuis te 's Hertogenbosch. In september 2011 startte zij met de vooropleiding Interne Geneeskunde in het Ikazia Ziekenhuis te Rotterdam (opleider: dr. A.A.M. Zandbergen). Gezien de opgedane ervaring op de Thoraxchirurgie en Spoedeisende Hulp, kreeg zij van de MSRC een jaar korting op de vooropleiding. In december 2012 startte ze in het Erasmus Medisch Centrum te Rotterdam aan het vervolg van haar opleiding tot Maag,- Darm- en Leverarts (opleider: dr. R.A. de Man)