CT-colonography in population-based colorectal cancer screening

de Haan, M.C.

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Chapter

Introduction and outline of the thesis
Introduction
Colorectal cancer (CRC) is the second most prevalent cause of cancer-related mortality in Europe\(^1\). In the Netherlands, CRC is the second most common cause of cancer, after breast cancer in women, while in men it is the third most common form of cancer, after lung cancer and prostate cancer\(^2\). Approximately 5% to 6% of the Dutch population develops CRC during lifetime\(^2\). The 5-year survival rate for patients with stage I CRC - in which the tumour is confined to the bowel wall - is 94%, while the survival rate of patients with distant metastases (stage IV) decreases to 8%\(^2\).

The large majority of colorectal cancers develop from adenomatous polyps, benign precursors with a relatively long premalignant phase\(^3\). Polyps arise from the normal inner lining of the colon. They can be roughly divided in adenomatous lesions and serrated lesions (hyperplastic polyps and serrated adenomas). Some of these lesions have a tendency to develop into a malignant tumour. The adenoma-carcinoma pathway is well-known and it is estimated that this pathway takes at least 10 years \(^4\). However, not all adenomatous lesions will develop into CRC. The tendency to become malignant is higher for adenomas of 10 mm or larger, but also for adenomas with at least 25% of villous histology and/or with high-grade dysplasia: known as advanced adenomas\(^3\). Through colorectal cancer screening programs, CRC can be detected in an earlier phase and CRC precursors can be detected and removed, which eventually leads to a decrease in CRC incidence and CRC related mortality\(^5\)-\(^7\).

Surveillance and colorectal cancer screening
Known risk factors for CRC are a personal history of adenomas or CRC, a personal history of inflammatory bowel disease, a personal diagnosis of familial adenomatous polyposis or Lynch syndrome, and a positive family history for CRC. According to the American Society for Gastrointestinal Endoscopy (ASGE), approximately 30% of the population must be considered as high risk individuals because they have one or more of these risk factors for CRC. These individuals should be offered surveillance, i.e. regular examinations at fixed time-intervals. The remaining 70% of the population are considered to be at average risk\(^9\).

The ASGE guideline states that screening for adenomatous polyps and CRC should be offered to all men and women at average risk, starting at the age of 50\(^9\). Colorectal cancer screening is also recommended in several other CRC screening guidelines, published by different organisations like the
American Cancer Society, the U.S. Multi Society Task Force on Colorectal Cancer, the American College of Radiology\textsuperscript{10}, and the American College of Gastroenterology\textsuperscript{11}. Also outside the United States screening for CRC is advocated, e.g. by the Asia Pacific Working Group on Colorectal Cancer\textsuperscript{12} and recently by the European Union\textsuperscript{13}.

Population-based screening for CRC is already performed or implemented in the United States of America and several European countries, like the UK and Italy. Screening becomes more and more accepted, although no consensus exists on the preferred screening method\textsuperscript{13,14}. Potential CRC screening methods fall into two categories: stool-based screening tests and structural examinations\textsuperscript{15}.

Stool-based screening tests are based on the principle of detecting blood, as do the guaiac faecal occult blood test (gFOBT) and faecal immunochemical test (FIT), or on the principle of detecting DNA markers in stool, with faecal DNA tests. Faecal occult blood tests are non-invasive tests, simple to perform and relatively cheap, but have a relatively low sensitivity for advanced adenomas and CRC\textsuperscript{16}. In most cases stool-based screening tests become only positive in subjects with relatively large adenomas or CRC\textsuperscript{8}. Stool-based screening tests therefore need to be repeated once every year or two years. Stool tests also have a tendency to result in a relatively high number of false positives in, for example, patients with haemorrhoids, leading to unnecessary referrals for colonoscopy\textsuperscript{17,18}. Faecal DNA tests are currently under development and relevant clinical data are not yet available.

Structural exams like flexible sigmoidoscopy, double contrast barium enema (DCBE), colonoscopy and computed tomography colonography (CT-colonography) visualize the colon and aim to detect both cancerous lesions and polyps in an early phase\textsuperscript{13}. Structural exams are more accurate for the detection of advanced neoplasia, but are invasive tests at relatively high costs.

**Colonoscopy versus CT-colonography**

Colonoscopy is widely accepted as the reference standard for detection of advanced adenomas and CRC and is currently in use for CRC screening in some countries, such as Poland, Germany and the United States. Previous tandem-colonoscopy studies have shown that colonoscopy misses only 2.1\% of adenomas of 10 mm and larger\textsuperscript{19}. During colonoscopy, the endoscopist visualizes the colon wall from the inside using a flexible tube with a small camera on the end. Before the examination, bowel cleansing is performed...
by the participant at home, drinking approximately 2 litres of laxatives and 2 litres of clear fluid - depending on the institutional standard.

Colonoscopy has the advantage that polyps can be removed during the same procedure in most cases. When the lesion is large or when the lesion has features suggestive for invasive growth (i.e. malignancy), the endoscopist may decide to discuss further treatment after the diagnostic endoscopy.

Compared to stool tests, screening colonoscopy has the advantage that it can be repeated with long intervals (i.e. 10 years after a negative colonoscopy), as it has been shown that the risk for CRC remains low for many years after a negative screening colonoscopy\(^2\). The most important disadvantages of colonoscopy are that it is an invasive technique and that patients need to be prepared with an extensive bowel preparation. Both factors make colonoscopy a more burdensome examination than stool tests. In addition, colonoscopy has a complication rate of 0.1% to 0.3%. The majority of these complications consist of post-polypectomy bleeding and perforation\(^2\).

CT-colonography might be a valuable alternative for colonoscopy, as it is less invasive. During CT-colonography, a soft and flexible, small-calibre catheter is inserted into the rectum and carbon dioxide (\(\text{CO}_2\)) is insufflated into the bowel to open it and prevent it from collapsing. Subsequently, the patient is scanned in the supine and prone position using a computed tomography scanner. When the distension of the bowel is inadequate in one of the two scan positions or a possible lesion is covered by faecal material, the opposite position can be helpful to visualize the entire colon. Studies showed that, when used as a screening technique for CRC in a screening population, CT-colonography misses 10% of patients with adenomas of 10 mm and larger and/or CRC\(^2\).

Like colonoscopy, CT-colonography also visualizes the entire colon. In addition, CT-colonography can be performed with a more limited bowel preparation, consisting of three bottles of 50 ml iodinated contrast agent. This non-cathartic bowel preparation also induces, however, diarrhoea, as most iodinated contrast agents are hyperosmotic and attract water to the bowel.

One of the most important disadvantages of CT-colonography is the need for a subsequent colonoscopy when possibly relevant lesions are detected. Colonoscopy is needed to remove polyps and/or to provide a histopathological diagnosis of polyps and cancer. The use of ionizing radiation
with CT-colonography may also induce the development of radiation-related cancers. The lifetime risk decreases when lower radiation doses are used. Nowadays, most CT-colonography examinations are performed with low-dose scan protocols, decreasing the risk of developing a radiation-induced cancer\textsuperscript{23}. Gonzalez et al estimated that for each radiation-induced cancer, 24 CRCs would be prevented when CT-colonography would be performed with a 5-years screening\textsuperscript{24}. These estimations were based on an estimated mean effective dose of 8 mSv for women and 7 mSv for men.

Additionally, the cost-effectiveness of CT-colonography screening can be a reason for concern. It is often debated whether the detection of extracolonic findings is an advantage or a disadvantage. It will probably lead to a substantial increase in the costs associated with CT-colonography screening, but might also lead to a decrease in costs that would have been associated with a later discovery of the particular findings.

Studies on colorectal cancer screening using gFOBT, FIT or sigmoidoscopy

In deciding which of the above described techniques is most favourable, it is not enough to compare the accuracy of a test. The diagnostic yield of a screening program, defined as number of invitees with relevant (precursor) lesions per 100 invitees, is not only depended on the sensitivity of the specific screening test, but also on the attendance. In case of colorectal cancer screening for example, invasive screening tests like colonoscopy and CT-colonography are more sensitive than non-invasive stool-based tests. However, invitees most likely expect a lower burden of stool-based screening tests. This difference in expected burden will probably be reflected in differences in participation (attendance rates). Therefore, a less burdensome screening test with lower sensitivity might result in a higher diagnostic yield per 100 invitees compared to a more burdensome screening test with higher sensitivity.

Most previous studies (performed outside the Netherlands) on the attendance and diagnostic yield of gFOBT and FIT screening in an average risk population have asked invitees to perform both screening tests\textsuperscript{25-28}. This might have induced a selection bias in favour of highly motivated patients. Only one non-randomised study performed in Australia, offered invitees a choice between gFOBT screening, FIT screening, or both\textsuperscript{29}. Overall participation rate in that study was 36\%, with a significantly higher participation in FIT screening compared to gFOBT screening (OR 1.9, 95\% CI 1.6 to 2.2). In 1.4\% of gFOBT participants and in 3.3\% of FIT participants, advanced neoplasia was detected during follow-up colonoscopy. After adjusting for differences

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in baseline characteristics, the effect on diagnostic yield appeared to be non-significant (OR 2.4, 95% CI 0.85 to 6.98). gFOBT screening has proven to decrease CRC related mortality by 16%. Data on the effect of FIT on CRC related mortality are lacking, but it is conceivable that this technique will also lead to a decrease in CRC related mortality.

Previous studies of sigmoidoscopy screening, performed in Italy and the UK, randomised invitees after a preselection of average risk subjects by the general practitioner or after contacted invitees had indicated on a questionnaire that they were interested making a true evaluation of attendance rates impossible. In the English study, 170,432 men and women were randomly allocated to a group invited for sigmoidoscopy screening or to the control group, after they had indicated on a previous questionnaire that they would accept an invitation for screening. Seventy-one percent of the invitees participated in sigmoidoscopy screening. That study showed – after a 10 year follow-up period – that a once-only sigmoidoscopy screening in selected individuals decreased CRC related mortality by 31%.

In the last few years, several large invitation-based CRC screening trials have been performed in the Netherlands, comparing the participation rate and diagnostic yield of gFOBT, FIT and sigmoidoscopy screening. Invitees in these studies were not preselected by general practitioners, but randomly assigned to one of the screening techniques after their personal data had been retrieved from the Dutch population registry, followed by an invitation by mail. The Dutch participation rates for gFOBT and FIT screening, defined as number of participants relative to the total number of invitees, were 47% and 59% to 60%, respectively, while sigmoidoscopy screening had a participation rate of 30%. Although fewer invitees participated in sigmoidoscopy screening compared to gFOBT and FIT screening, sigmoidoscopy screening resulted in a higher diagnostic yield for advanced neoplasia of 2.2 per 100 invitees, compared to 0.6 and 1.4 to 1.5 per 100 invitees in gFOBT and FIT screening, respectively.

Studies on colonoscopy and CT-colonography screening
Both colonoscopy and CT-colonography are interesting alternatives for CRC screening, as both techniques are highly accurate in detecting (advanced) adenomas and CRC. However, as indicated before, the diagnostic yield of a screening technique not only depends on its accuracy but also on the participation rate. Until now, only one study has been published comparing the participation rate and diagnostic yield of colonoscopy and
CT-colonography screening. This concerns a small Australian randomised controlled (community-based) screening trial\textsuperscript{37}. In that study, 16\% of colonoscopy invitees participated compared to 18\% of CT-colonography invitees. However, invitees who met the exclusion criteria were excluded before the analysis (no intention-to-treat analysis), thereby artificially increasing the participation rate. Advanced neoplasia was detected in 8.4 per 100 colonoscopy participants and 9.0 per 100 CT-colonography participants, respectively.

Two Italian studies have reported participation rates for colonoscopy screening ranging from 10\% to 27\%, although the screenees in these studies were not invited by mail, but preselected before randomisation by their general physicians\textsuperscript{31,38}. Other studies reporting on diagnostic yield of colonoscopy in an average risk population were not invitation-based. These studies reported a diagnostic yield for advanced neoplasia that ranged from 3.4 to 8.9 per 100 participants\textsuperscript{39-43}.

With respect to CT-colonography screening, the Australian study was the only one that evaluated the participation rate\textsuperscript{37}. Most previous studies on CT-colonography in screening were designed to determine the accuracy of CT-colonography in the detection of all polyps, adenomas and/or CRC in a screening population\textsuperscript{22,44-48}. Participants in these studies underwent both colonoscopy and CT-colonography. Besides the Australian study, only one non invitation-based study evaluated the referral rate of CT-colonography for colonoscopy and the diagnostic yield for advanced neoplasia. In that study, 7.9\% of participants were referred for colonoscopy and in 3.2\% of participants advanced neoplasia was detected\textsuperscript{43}. In that study, participants were referred for colonoscopy when the radiologist detected lesions of 10 mm and larger on the CT-colonography images. However, participants with lesions of 6-9 mm were offered a choice between a surveillance CT-colonography and referral to colonoscopy. It is unknown, how many of these participants chose for colonoscopy.

Thus, no previous large randomised controlled trials have been reported that studied the participation rate and diagnostic yield per 100 invitees of colonoscopy and CT-colonography screening within an invitational, population-based CRC screening program, using an intention-to-treat analysis.

**Outline of the thesis**
The research in this thesis relies primarily on data collected in the COCOS
trial. The COCOS trial - colonoscopy or CT-colonography for screening – was designed as a randomised controlled trial to investigate and compare the participation rate and diagnostic yield of an invitational, population-based colorectal screening program, using either colonoscopy or CT-colonography for primary screening within the Dutch situation. Gathering these data would make it possible to compare these results with those from earlier Dutch studies investigating the diagnostic yield of gFOBT, FIT, and sigmoidoscopy screening within a similar population in the Netherlands. The trial also provided the possibility to evaluate the expected and perceived burden of colonoscopy and CT-colonography screening techniques and to evaluate whether invitees made an informed decision on participation. In addition, the trial made it possible to collect data on reasons for participation and non-participation, and to calculate the unit cost of colonoscopy and CT-colonography when used as a primary screening technique in colorectal cancer screening.

At the beginning of the study, we performed a meta-analysis to estimate the diagnostic value of CT-colonography for the detection of advanced neoplasia in an average risk population aged 50 to 75 years. We considered subjects to be at average risk when they had no symptoms of CRC, no personal history of adenomatous polyps or CRC, no personal history of inflammatory bowel disease and no family history of advanced neoplasia. Previous meta-analyses comparing the diagnostic value of CT-colonography and colonoscopy had included both average risk and high risk participants, which can lead to an overestimation of the per patient sensitivity in a screening population. In high risk subjects, the radiologist may be more focused on the detection of polyps, using a lower positivity threshold in reading the images, as he knows that the person is at increased risk for the development of lesions. We therefore performed a meta-analysis, including predominantly average risk subjects, to estimate the diagnostic value of CT-colonography in screening. The results of this systematic review are described in Chapter 2.

Chapter 3 outlines the protocol of the COCOS trial, providing a detailed description of the primary and secondary aims as well as the methods of the study. Chapter 4 focuses on differences in participation and diagnostic yield of colonoscopy and CT-colonography screening, within a large population-based, invitational CRC screening trial (the COCOS trial). Chapter 5 reports the results on differences in expected burden scores, as indicated by the colonoscopy and CT-colonography invitees, and differences in perceived burden scores indicated by the participants. Because of the less invasive nature of CT-colonography and the limited bowel preparation that was used in our
study, we expected that colonoscopy invitees would expect a higher burden, which might be reflected in a higher participation rate in the CT-colonography group. In addition, we expected that colonoscopy participants would experience the examination as more burdensome compared to CT-colonography participants.

Within the CT-colonography group we compared the experienced burden and symptoms that occurred during the performance of the examination, between participants receiving butyl scopolamine (Buscopan, Boehringer-Ingelheim, Ingelheim, Germany) and participants receiving glucagon hydrochloride (GlucaGen, Novo Nordiks A/S, Bagsvaerd, Denmark) as bowel relaxant. Buscopan has shown to improve bowel distension significantly when compared to placebo, while the relaxing effect of GlucaGen still remains controversial. However, each bowel relaxant also has its side effects. Depending on the nature and frequency of these side effects, it may be possible to decide whether the downsides of these bowel relaxants outweigh the advantages. The purpose of this study was to estimate the frequency of side effects during the examination, to investigate differences in experienced pain during insufflation of CO₂ and to examine whether there was any difference in experienced burden between the group of participants receiving Buscopan and the group of participants receiving GlucaGen. The results are described in Chapter 6.

In invitational screening programs, the information leaflets and letters should provide enough decision-relevant information to allow invitees to make an informed decision on participation. An informed decision is based on adequate decision-relevant knowledge, leading to a behaviour that is consisted with the personal attitude towards participation. In Chapter 7 we evaluated whether colonoscopy participants and non-participants and CT-colonography participants and non-participants made an informed decision on participation in the COCOS trial.

Understanding the reasons for participation and non-participation can be of help in the design of future leaflet programs, to reach certain subgroups of invitees that might accept or decline the invitation for the wrong reasons, such as those who decline the invitation because of absence of CRC related symptoms. For the purpose of this study a previously validated questionnaire was sent to all invitees. The results are outlined in Chapter 8.

As stated before, one of the major concerns of population-based CRC screening using primary CT-colonography are the associated costs. One way to lower the costs might be to replace the radiologist by a technician as primary
CT-colonography reader. Previous studies showed that technologists can be adequate CT-colonography readers. To evaluate whether technologists are able to reach a comparable diagnostic yield per 100 participants compared to the radiologists in population-based CRC screening, all CT-colonography examinations in the COCOS trial were read by one radiologist and by two out of four trained technologists. The results of this study are presented in Chapter 9.

Previous cost-effectiveness studies on colonoscopy and CT-colonography based their unit cost for CT-colonography on the average reimbursement costs for abdominal and pelvic computed tomography or on the average reimbursement costs for colonoscopy. Details on the actual costs for CT-colonography screening were lacking, therefore we calculated the actual costs for CT-colonography when used in a primary CRC screening setting. The results are displayed in Chapter 10 of this thesis.

The last decade, several CRC screening guidelines originating from the United States, Asia and Europe have indicated that screening for CRC (and advanced adenomas) should be offered to all men and women at average risk, starting at the age of 50. CT-colonography might be a valuable alternative for population-based screening, as it has a high sensitivity of 88% for advanced neoplasia of 10 mm and larger. However, next to the sensitivity of a screening technique, also other factors like difference in burden, cost-effectiveness and effect on (disease specific) mortality should be taken into account. Chapter 11 reviews important issues that are relevant in finding the answer on the following question ‘Does CT-colonography have a role for population-based colorectal cancer screening?’

A summary of the thesis is provided in Chapter 12 and 13, including a general discussion of our findings and the implications for the future.
References


