Endoscopic Screening for Colorectal cancer - Quality and Effectiveness

Dissertation for the degree of Philosophiae Doctor (PhD)

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Table of Contents

To pappa. I wish you could read this.

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Frederik Emil,

December 2022, Oslo (I know, the plan was to write this in Skjåk.)

Abbreviations

BBPS	Boston Bowel Preparation Score
CI	Confidence interval
CRC	Colorectal cancer
CT	Computer tomography
FIT	Fecal immunochemical testing
FOBT	Fecal occult blood testing
gFOBT	Guaiac-based fecal occult blood testing
iFOBT	Immunologic fecal occult blood testing (same as FIT)
IRR	Incidence rate ratio
ISRCTN	International Standard Randomized Controlled Trial Number Registry.
MRR	Mortality rate ratio
NNS	Number needed to screen
NORCCAP	Norwegian Colorectal Cancer Prevention - A randomized controlled trial evaluating flexible sigmoidoscopy screening for colorectal cancer in Norway
NordICC	Nordic-European Initiative on Colorectal Cancer
PLCO	Prostate, Lung, Colorectal and Ovarian – a randomized controlled screening trial in the US
PYr	Person-years
RCT	Randomized controlled trial
SCORE	Screening for Colon REctum trial - a randomized controlled trial evaluating flexible sigmoidoscopy screening for colorectal cancer in Italy
UK	United Kingdom
UKFSST	UK Flexible Sigmoidoscopy Screening Trial - A randomized controlled trial evaluating flexible sigmoidoscopy screening for colorectal cancer in the United Kingdom
US	United States
WHO	World Health Organization

Papers included in the thesis

Paper 1: **15-Year Benefits of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality: A Pooled Analysis of Randomized Trials**

Frederik E Juul, Amanda J Cross, Robert E Schoen, Carlo Senore, Paul Pinsky, Eric Miller, Nereo Segnan, Kate Wooldrage, Paulina Wieszczy-Szczepanik, Paola Armaroli, Kjetil K Garborg, Hans-Olov Adami, Geir Hoff, Mette Kalager, Michael Bretthauer, Magnus Løberg, Øyvind Holme

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Paper 2: **15-year Effectiveness of Colonoscopy Screening on Colorectal Cancer Incidence and Mortality - Simulation Analysis of Four Sigmoidoscopy Trials**

Frederik E Juul, Amanda J Cross, Robert E Schoen, Carlo Senore, Paul Pinsky, Eric Miller, Nereo Segnan, Kate Wooldrage, Paulina Wieszczy-Szczepanik, Paola Armaroli, Kjetil K Garborg, Hans-Olov Adami, Geir Hoff, Mette Kalager, Michael Bretthauer, Øyvind Holme, Magnus Løberg

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Paper 3: **Rates of Repeated Colonoscopies to Clean the Colon from Low and High Risk Adenomas - Results from the EPoS trials**

Frederik E Juul, Kjetil Garborg, Eugen Nesbakken, Magnus Løberg, Paulina Wieszczy, Joaquin Cubiella, Mette Kalager, Michal F. Kaminski, Rune Erichsen, Hans-Olov Adami, Monika Ferlitsch, Siv K.B. Furholm, Ann Zauber, Enrique Quintero, Marek Bugajski, Øyvind Holme, Evelien Dekker, Rodrigo Jover, Michael Bretthauer, for the EPoS study group

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1 Thesis summary

Background

Colorectal cancer (CRC) accounts for more than 1 900 000 new cases and 935 000 deaths world-wide each year. Most CRC cases are diagnosed in individuals aged 65 to 74 years and risk of developing CRC before age 75 is 5.1% in men and 3.5% in women. Randomized trials have demonstrated that sigmoidoscopy screening reduce CRC incidence by 18% to 26% and CRC mortality by 21% to 30%, but there is uncertainty to whether CRC screening effectiveness differ by sex or age.

Screening programs across the world have switched from sigmoidoscopy screening to primary colonoscopy screening due to the assumption of a better colonoscopy screening effect in the proximal colon. However, the only randomized colonoscopy screening trial with published follow-up results showed an overall effectiveness on CRC incidence similar to that of sigmoidoscopy screening trials and did not report CRC mortality or CRC incidence by sex. No clinical trial have directly compared sigmoidoscopy screening to colonoscopy screening.

The quality of the colonoscopy procedure (e.g. in colonoscopy screening or as follow-up to sigmoidoscopy) is key to the effectiveness of screening and a high-quality procedure is a prerequisite for the patient to enter post-polypectomy surveillance. The number of colonoscopies needed to remove all colon polyps, before the patient can enter surveillance, is unknown.

The aim of the thesis is to investigate comparative effectiveness and performance of colorectal cancer screening and gastrointestinal endoscopy service.

Methods

Investigators of the four existing randomized trials comparing an invitation to sigmoidoscopy screening to usual care (i.e. no screening invitation) shared yearly participant data (number of individuals at risk, CRC cases and deaths), by sex, randomization group and 5-year age group. We pooled the data to estimate the 15-year screening effectiveness on CRC incidence and mortality. Next, we estimated the additional benefits of switching from sigmoidoscopy screening to colonoscopy screening by performing a simulation meta-analysis using data from the four sigmoidoscopy screening trials. Finally, we estimated the number of colonoscopies needed to

achieve a colon free of polyps in participants included trials on post-polypectomy surveillance (EPoS I and II trials). Proportions of patients with two or more colonoscopies were calculated separately for patients with low- and high-risk adenomas, and by country, endoscopy center and individual endoscopist.

Results

Our pooled analysis showed that invitation to sigmoidoscopy screening led to a relative reduction in CRC incidence by 21% and CRC mortality by 20%. Sigmoidoscopy screening effectiveness was lower in women than men and invitation to screening did not reduce CRC mortality in women. Our study is the first to demonstrate an effect of CRC screening on all-cause mortality (2% reduction).

Our second paper showed that colonoscopy screening can reduce CRC incidence and mortality even more than sigmoidoscopy, by approximately 7 percentage points, but three quarters of the colonoscopy screening effect is already achieved by sigmoidoscopy screening. In a population that already receive invitation to sigmoidoscopy screening, the number needed to switch to colonoscopy screening to prevent one CRC case were 560 individuals, and to prevent on CRC death; 1611 individuals. Numbers needed to switch to colonoscopy to prevent one CRC case or death were higher in women than men.

Based on data from 15 581 participants at 38 endoscopy centers in five European countries, 1.5% (n=101) of patients with low-risk adenomas and 9.8% (n=825) of patients with high-risk adenomas were scheduled for two or more colonoscopies before entering surveillance. The proportion of patients varied between centers, from 0% to 11.8% in low-risk adenoma patients and from 0% to 63.9% in high-risk adenoma patients.

Conclusions

Colorectal cancer screening and surveillance are dependent on each other as parts of an individuals' treatment path and put demand on the same endoscopy service resources. Our studies show that sigmoidoscopy screening have a long-lasting effect on CRC incidence and mortality, but the effect is less inn women than in men. The additional benefits of switching to colonoscopy is limited. Further, our work revealed substantial variations in number of colonoscopies needed to remove all colon polyps, before entering post-polypectomy surveillance.

2 Vitenskapelig sammendrag

Bakgrunn

På verdensbasis forekommer 1 900 000 nye tarmkrefttilfeller hvert år, og i samme tidsintervall dør 935 000 av sykdom. De fleste tilfeller av tarmkreft diagnostiseres hos personer i alderen 65 til 74 år, og risikoen for å utvikle tarmkreft før 75 år er 5,1% hos menn og 3,5% hos kvinner. Randomiserte studier har vist at sigmoidoskopiscreening reduserer forekomsten av tarmkreft med 18% til 26% og dødeligheten med 21% til 30%, men det er usikkerhet om effekten er ulik for ulike kjønn eller aldersgrupper.

Screeningprogram over hele verden har gått over fra sigmoidoskopiscreening til primær koloskopiscreening, med antakelsen om at screening med koloskopi har en bedre effekt i den proksimale tykktarmen. Imidlertid viste de første resultatene fra en randomisert studie på koloskopiscreening at effekten på tarmkreftforekomsten tilsvarte den en hadde sett i tidligere screeningstudier med bruk av sigmoidoskopi. Koloskopiscreeningstudien rapporterte ikke tall på tarmkreft-spesifikk dødelighet eller tarmkreftforekomst for ulike kjønn. Ingen kliniske studier har direkte sammenlignet sigmoidoskopiscreening med koloskopiscreening.

Kvaliteten på koloskopi-undersøkelsen (f.eks. som primær screeningundersøkelse eller oppfølging i sigmoidoskopiscreening) er nøkkelen til effektiviteten av screening, og en høykvalitets-prosedyre er en forutsetning for at pasienten kunne starte overvåkningsperioden etter polyppfjerning. Det er ikke kjent hvor mange koloskopier som trengs (på gruppenivå) for å fjerne alle kolonpolypper hos en pasient, før hen starter overvåkningsperioden (*eng: surveillance*).

Hensikten med denne avhandlingen er å sammenlikne effektivitet og kvalitet av tarmkreftscreening og gastrointestinal endoskopi.

Metoder

Forskningsgruppene ansvarlige for de fire eksisterende randomiserte studiene som sammenligner invitasjon til sigmoidoskopiscreening med ingen invitasjon, delte deltakerdata per oppfølgingsår, etter kjønn, randomiseringsgruppe og 5-års aldersgrupper. Dataene ble brukt til å estimere effektiviteten av screening på tarmkreftforekomst og dødelighet etter 15 års oppfølgingstid.

Deretter benyttet vi dataene fra de fire sigmoidoskopiscreening-studiene til å utføre en simuleringsanalyse, for å estimerte den ekstra gevinsten av å bytte til screening med koloskopi. Til slutt estimerte vi antall koloskopier som var nødvendig for å fjerne alle kolonpolypper hos pasienter i de to studiene på overvåkning etter polyppfjerning (EPoS I og II studiene). Andel av pasienter med to eller flere koloskopier ble beregnet separat for deltakere med lav- og høyrisikoadenomer, og etter land, endoskopisenter og individuell endoskopør.

Resultater

Vår samleanalyse viste at invitasjon til screening med sigmoidoskopi førte til en relativ reduksjon i tarmkreftforekomst på 21% og reduksjon i tarmkreftdødelighet på 20%. Effektiviteten var lavere hos kvinner enn menn, og invitasjon til screening reduserte ikke tarmkreftdødeligheten hos kvinner. Vår studie er den første som viser en effekt av tarmkreftscreening på totaldødelighet (2% reduksjon). Vår andre artikkel viste at koloskopiscreening kan redusere tarmkreftforekomst og -dødelighet ytterligere, med omtrent 7 prosentpoeng, men tre-fjerdedeler av effekten ved koloskopiscreening er allerede oppnådd med sigmoidoskopiscreening.

I en populasjon som allerede mottar invitasjon til sigmoidoskopiscreening, var antall individer som må bytte til koloskopiscreening for å forhindre ett tarmkrefttilfelle 560 individer, og for å forhindre ett tarmkreftdødsfall; 1611 individer. Antallet som måtte bytte til koloskopi for å forhindre ett tilfelle av tarmkreft eller død som følge av tarmkreft var høyere hos kvinner enn menn.

Basert på data fra 15 581 deltakere fra 38 endoskopisentre i fem europeiske land, gjennomførte 1,5% (n=101) pasienter med lavrisikoadenomer og 9,8% (n=825) pasienter med høyrisikoadenomer to eller flere koloskopier før kunne starte overvåkningsperioden etter fullført fjerning av tarmpolypper. Andelen pasienter varierte mellom endoskopisentrene, fra 0% til 11,8% hos pasienter med lavrisikoadenomer og fra 0% til 63,9% hos pasienter med høyrisikoadenomer.

Fortolking

Screening og overvåking av tykktarmskreft er avhengig av hverandre som en del av et individs behandlingsforløp, og legger beslag på de samme endoskopi-ressursene. Våre studier viser at sigmoidoskopiscreening har en langvarig effekt på tarmkreftforekomst og -dødelighet, men

effekten er mindre hos kvinner enn hos menn. Å bytte til koloskopi gir en ytterligere, men begrenset tilleggs-gevinst. Videre viste resultatene våre en betydelige variasjoner i antall koloskopier som var nødvendige for å fjerne alle tykktarmspolypper, før pasienten går inn overvåkningsperioden etter kolonpolyppfjerning.

3 Introduction

3.1 Colorectal cancer

3.1.1 Epidemiology

With more than 1 900 000 new cases each year, colorectal cancer (CRC) is the third most common cancer in the world.(1) CRC cause 935 000 deaths each year, putting the disease on a grim second place in terms of cancer mortality. Nearly 60% of CRC cases are in the distal colon (i.e. descending and sigmoid colon) or rectum.(2)

Both genetic and environmental factors are involved in the development of CRC. Two important risk factors are age and sex; most CRC cases are diagnosed in individuals aged 65 to 74 years, and worldwide the risk of developing CRC before age 85 are 5.1% in men and 3.5% in women.(3) Other known risk factors are family history of CRC, overweight, inflammatory bowel disease, tobacco use, and high consumption of alcohol, red- or processed meat.(1, 4) Physical activity and a diet rich in fiber, in addition to aspirin and non-steroid anti-inflammatory drugs have been shown to be protective.(5)

There are large regional differences in CRC incidence and mortality, which are especially high in high-income countries in the northern hemisphere (i.e. North America and Europe), Australia and New Zealand.(6) Women in Norway have a cumulative risk of CRC of 8.4% (before age 85), which is the highest in the world (in women).(3, 7) The main contributor to the high CRC incidence and mortality in high-income countries is uncertain, but life-style (e.g. dietary habits) and an ageing population have been proposed as key factors.(8) CRC incidence and mortality are stable or declining in high-income countries but is expected to increase worldwide due to a predicted increase in low-income countries.

3.1.2 Pathogenesis

Most CRC are adenocarcinomas and arise from cells in the colon mucosa, a process that is believed to take 10-15-years and occur because of accumulating genetic and epigenetic changes in mucosal cells.(8) 70-90% of cancers develop in the traditional adenoma-carcinoma pathway, in which the cells evolve into a precancerous adenoma and further into cancer that penetrate the basal membrane and gain the potential to metastasize. Adenomas are visible in the colon as polyps, but not all polyps are adenomas.

Adenomas can be classified according to macroscopic appearance (pedunculated, flat, sessile or depressed), dysplasia (low- or high-grade) and growth pattern (tubular, villous or tubulovillous).(9) Most adenomas do not progress to cancer. An individual's risk of developing CRC increase if he/she has large adenoma(s), many adenomas, or adenomas with ≥25% villous architecture or high-grade dysplasia.(10-12)

It has been shown that there are genetic differences in proximal versus distal colon cancer.(8) There are, for example, more often hypermethylation and microsatellite instability in proximal, compared to distal, colon cancer.(13) Additionally, there are biological and anatomical differences (e.g. blood supply) between proximal and distal colon cancers relevant for diagnosis and disease progression (incl. metastasis).

3.2 Screening

3.2.1 Screening principles

The purpose of screening in medicine is to detect a medical condition (i.e. disease or those who are at higher risk of developing disease) in presumptively healthy individuals.(14, 15) In other words, screening differs from diagnosis of disease in patients with symptoms because screened individuals do not have any symptoms of the disease. Examples of established screening programs in Norway are blood tests for metabolic diseases in newborns and mammography for breast cancer.(16, 17)

To justify the resources needed to conduct screening, certain criteria should be met. First, the disease screened for should be an important health problem. Second, the disease should have a non-symptomatic early or latent stage that is detectable with an available test that is acceptable to the screening population. Third, screened individuals with identified disease or high risk of developing disease should have the possibility to receive an acceptable treatment, to cure or limit the progression of disease that is already present, or to prevent the disease from developing. Importantly, screening should be a continuous process, not just a test,(18) and a good screening program needs to take burdens (including costs) and harms of the whole process into account.(14, 15)

The effectiveness (i.e. "the ability of an intervention to have a meaningful effect on patients in normal clinical conditions" (19)) of screening depends on several factors, and among the important factors are the prevalence of the condition screened for in the screening population and the quality

(performance) of the screening test. Key elements of the test's quality are its ability to detect the condition (test sensitivity) and identify healthy individuals (test specificity), which are not influenced by population prevalence, but depend on the screening method (at a given threshold for a positive test).(14, 20)

The prevalence of the condition in the screened population depend on who are invited and attend screening. Screening in medicine can be applied at a population level, or be targeted at a specific population due to known risk factors such as age. This increases the prevalence of the condition in the screening population, resulting in a higher positive predictive value (i.e. probability that a positive screening test results is true).(14, 21) The prevalence of the condition in the screened population will also depend on the attendance rate, meaning if invited individuals attend screening or not. Obviously, screening cannot prevent disease in individuals who do not attend. High attendance is preferred because, in theory, higher attendance means that more individuals with the condition (who benefit from screening) are screened.

Screening attendance varies considerably between groups of people (e.g. socioeconomic class), countries and time periods, even for screening programs directed towards the same disease.(22) Among factors that influence attendance rate are the type of disease, screening invitation method, ease-of-access to the recommended test (e.g. economical cost for the patient and long travel to test site versus home testing) and how uncomfortable the test is.(23, 24) Individuals who participate to screening may have different characteristics and risk of disease, compared to those who don't participate screening (non-attenders).(25-27)

3.2.2 Cancer screening

Cancer is an important health problem, accounting for nearly every sixth death,(28) and often develop (asymptomatically) over years. Thus, cancer types (and their precursors) that can be detected and treated are possible diseases that can be targeted in screening. One of the main goals of cancer screening is to reduce cancer mortality. In principle, cancer screening can reduce mortality through two mechanisms: early detection or prevention.(29) Early detection is when screening identifies individuals with cancer at an early stage, before the cancer has spread to lymph nodes or other organs. In general, cancer detected early are more feasible to treat with success than cancer detected later, when symptoms have developed (e.g. because symptomatic cancers demand more

invasive surgery, or have metastasized). Thus, early detected cancers have a better prognosis and fewer die of the disease. However, early detection screening cannot reduce cancer incidence, since detected cancers are already present, but may actually increase cancer incidence in the screening population due to overdiagnosis.(30)

Preventive screening, on the other hand, involves detection and removal of precursors to cancer. Fewer precursor lesions means less cancer, thus reducing incidence. Further, less cancer means less cancer related deaths, and consequently, lower cancer mortality.

3.2.3 Colorectal cancer screening

As previously described, CRC is a major health problem with a known asymptomatic precancerous stage, and individuals with CRC usually develop symptoms (e.g. rectal bleeding) when the cancer is at an advanced stage. The precancerous lesions can be identified and removed by endoscopy (sigmoidoscopy or colonoscopy) (see 3.2.4). Thus, CRC is an ideal target for preventive screening and several countries have implemented CRC screening programs.(31, 32)

There is no consensus on the optimal age for CRC screening in an average-risk population but most guidelines recommend screening individuals aged 50 to 74 years.(33) The rationale is that screening should be performed before most CRC are diagnosed, to be able to intervene at the adenoma or early-CRC stage. Some guidelines recommend screening from age 40 and do not have an upper limit for screening age.(34) Screening or other testing of individuals with known inflammatory bowel disease or family history of CRC is beyond the scope of the current thesis, which looks at CRC screening in individuals with no known risk factors (i.e. average-risk individuals).(35, 36)

Most CRC screening approaches are two-step processes, where individuals with positive initial screening tests are referred to colonoscopy for follow-up.(18, 36) There are several CRC screening tests available, each with their advantages and disadvantages.(32) Direct visualization tests (e.g. sigmoidoscopy) and stool based tests are the most studied, with up to 30 years of follow-up in the studies,(37) while most other proposed CRC screening tests lack data from randomized clinical trials.(8, 33)

3.2.4 Endoscopy

Endoscopy means to inspect the interior of a hollow organ in a patient, for example the urine bladder or gastrointestinal tract, with a tube (= "endoscope") that has a camera on its end. In addition to the camera, many endoscopes have parallel channels in the tube to take samples or do small invasive procedures (e.g. polyp removal) via the endoscope. There are two ways to enter the gastrointestinal tract with an endoscope: via the mouth (upper) or via the anus (lower). Upper endoscopy (e.g. gastroscopy) will not be described or discussed further as it is not relevant in CRC screening.

Sigmoidoscopy and colonoscopy are two lower endoscopy methods that enable the investigator to inspect the inside of the colon and rectum. The procedures require an advanced, flexible endoscope and are in most countries performed by trained physicians in specialized hospital departments (e.g. surgery or gastroenterology). A few countries like the United States (US), England and the Netherlands allow other health care personnel to perform the procedure.(38)

Colorectal cancer screening by endoscopy has the advantage of disease prevention (by adenoma removal) in addition to early diagnosis of cancer (e.g. by visualization and/or through biopsy of lesions). Screening with lower endoscopy can be performed once-only or as a repeated procedure, for example every 10 years.(33) Lower endoscopy are not only performed as part of a screening program, but are key tools in diagnosis and treatment of different gastrointestinal diseases such as inflammatory bowel disease or gastrointestinal bleeding.(39)

The procedures are not without risks, with colon perforation being the most severe procedure-related complication. The risk of colon perforation is higher with colonoscopy, compared to sigmoidoscopy, and have been reported to be from zero (of 3196 colonoscopies(40)) to 0.2% for diagnostic colonoscopies.(41, 42) The observed risk is higher following therapeutic colonoscopy but the estimates vary widely, from 0 to 5%, and are mainly based on studies conducted more than 10 years ago.(39, 41-44) Risk factors for colon peroration are older age and comorbid conditions (e.g. diverticular disease). Mortality in the event of colon perforation can be as high as 5%.(45)

A more common complication of lower endoscopy is bleeding, which can occur during or after the procedure.(45) The observed risk in older data were 0.008% for diagnostic colonoscopies and 2.24% for polypectomy by colonoscopy.(46, 47) A more recent overview discovered a trend towards reduced number of post-polypectomy bleeding from 2001 to 2015 (from 0.006% to 0.001%),(42)

while a screening trial with colonoscopies performed from 2009 to 2014 (the NordICC trial, see 3.2.6) observed post-polypectomy bleeding in 0.14% of participants.(48) Important risk factors for post-polypectomy bleeding are advanced age, use of anticoagulation or antiplatelet medication, or removal of large polyps in the proximal colon.(42, 49)

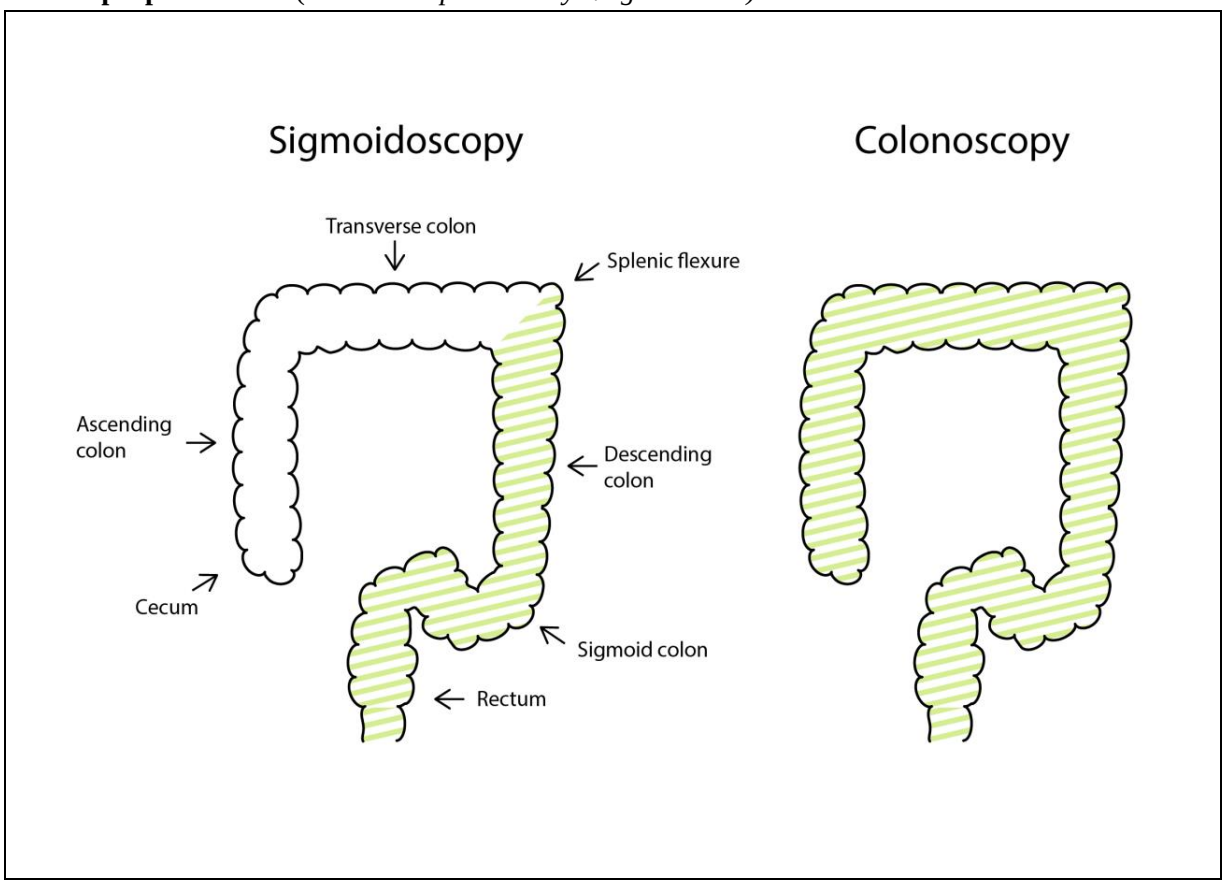
3.2.5 Sigmoidoscopy

In preparation to a sigmoidoscopy, the patient is allowed to eat a light breakfast the day of the procedure, before the patient's bowel is emptied with an enema ("bowel preparation") at home or at the hospital. The patient go to the endoscopy room after the bowel preparation and the endoscopist who perform the procedure is assisted by one or two nurses. Patients are usually awake during the procedure, which can be unpleasant to some, and more often in women than men.(50)

It is an advantage of sigmoidoscopy that the bowel preparation can be performed the same day as the procedure. The drawback is that most patient's colon is only partly emptied when they enter the endoscopy room. As a result, sigmoidoscopy usually allows the visualization of the rectum, sigmoid colon and descending colon (to the splenic flexure) (Figure 1, left), but is unable to inspect the proximal colon (i.e. transverse colon, ascending colon or cecum). Thus, there needs to be a synchronous sigmoidoscopy finding in the distal colon, resulting in a follow-up colonoscopy, to identify proximal adenomas or CRC.(51)

Indeed, observational studies and four randomized trials have demonstrated that sigmoidoscopy screening reduces CRC incidence by 18% to 26% and mortality by 21% to 30%, but the effect is limited to the distal colon.(52-57) One of the randomized trials did not find an effect on CRC incidence or mortality in women,(55) and a recent update from one of the other trials revealed a smaller reduction in CRC incidence among women (risk reduction: 1.34 per 10 000 person-years), compared to men (risk reduction: 4.28 per 10 000 person-years).(53) The latter trial also showed a greater risk reduction in older individuals (65-74 years), compared to younger individuals (55-64 years): 4.49 versus 1.85 per 10 000 person-years, respectively.(53) A meta-analysis of three of the randomized trials indicated no effect in women aged 60 years or older.(58)

Figure 1: Schematic illustration of the reach of flexible sigmoidoscopy (left) and colonoscopy (right) endoscopic procedures. (*Illustration provided by Jørgen Valeur)*



3.2.6 Colonoscopy

Colonoscopy utilizes the same instrument as in sigmoidoscopy, but involves a more thorough bowel preparation where one seeks to completely empty the patient's colon of fecal content. The patient cannot eat and only drink clear fluids before the procedure, starting from the evening before the procedure, and in addition needs to take an oral laxative. The laxative can be given as a one- or two-dose regimen of which the latter is recommended.(59) The extensive bowel preparation before colonoscopy means that most patients need to be close to a toilet from the evening before the procedure.

The described "full bowel preparation" in colonoscopy is also the procedure's advantage over sigmoidoscopy because it enables the endoscopist to investigate the colon lumen all the way to caecum and terminal ileum (Figure 1, right). The Boston Bowel Preparation Score (BBPS) is often used to quantify bowel preparation quality and is based on the endoscopist's assessment of each of

three colon segment (right colon, transverse colon, and left colon) from 0 (unprepared colon) to 3 (entire mucosa visible), to get a total score between 0 and 9.(60)

Colonoscopy, with its high sensitivity of 89-98%, is the gold standard for polyp and CRC detection.(32) In the United States, colonoscopy has become the primary CRC screening test.(33) Most other countries with CRC screening program reserve the procedure for individuals with a positive screening test (e.g. FIT or sigmoidoscopy) as part of a two-step screening process.(8, 36)

Until recently, the effect of primary colonoscopy screening on CRC incidence and mortality was estimated from observational and modelling studies, and a meta-analysis reported 69% CRC incidence reduction and 68% CRC mortality reduction.(61) Even though colonoscopy allows for the investigation of the proximal colon, the observed effect seems to be less pronounced in this part of the colon (compared to distal colon). Four randomized trials on primary colonoscopy screening exist, of which only The Northern-European Initiative on Colorectal Cancer (NordICC) trial has completed follow-up and published their results.(62-65) The NordICC trial's primary intention-to-treat analysis, comparing individuals invited to colonoscopy screening to individuals without a screening invitation, revealed a relative reduction in CRC incidence of 18% (risk reduction: 0.22 percentage points), but no statistical significant reduction in CRC mortality.(64) No clinical trial have directly compared sigmoidoscopy screening to primary colonoscopy screening.

3.2.7 Fecal occult blood tests

Visible blood in the stool can be the first symptom of CRC and is due to increased vascularization in cancer tumors.(66, 67) Early (pre-symptomatic) cancer and some adenomas may also bleed and fecal occult blood tests (FOBT) are able to detect the bleeding before it is visible to the human eye. Modern immunochemical FOBT-tests (iFOBT or FIT) are specific to human blood and do not necessitate diet restriction before testing.(68) Testing is typically repeated annually or biennially.(69) The advantage of FOBT is its non-invasiveness and that it can be performed without the patient having to go to a clinic. Still, attendance rate in FOBT screening programs seems to be only slightly higher than endoscopic methods.(69, 70) Disadvantages are the low sensitivity, resulting in false negative tests (not all cancers bleed and few bleed constantly) and that the test is less sensitive to detect adenomas.(71)

Several randomized trials have demonstrated an effect of FOBT tests on CRC mortality but these studies were not using FIT-tests.(72) The effect of FIT in CRC screening is based on observational studies and the assumption that FIT-tests are better due to its higher sensitivity and specificity compared to other FOBTs (e.g. guaiac FOBT). Three ongoing randomized trial aim to compare annual FIT to primary colonoscopy screening.(62, 63, 65) One of these trials have a third randomization arm (control group) without any screening invitation.(63)

3.2.8 Other tests considered for screening

There are many other CRC screening methods under current investigation.(33) Computed tomography (CT) colonography is good at detecting polyps 6 mm or larger and is non-invasive, compared to endoscopic methods.(73, 74) Yet, patients have to perform bowel preparation before the procedure and other disadvantages are limited availability, radiation exposure and risk of detecting incidental, extra-colonic findings (e.g. adrenal mass) that need follow-up.(33, 72) Stool tests for DNA-mutations or -methylation suspicious of cancer are suggested, and are being tested as stand-alone tests or in combination with colonoscopy or FIT to enhance test sensitivity.(75) These DNA-based test are expensive and have a more complicated sampling and analysis procedure, compared to existing FOBT methods which may reduce attendance rate.(76) Colon capsules with camera and tests based on blood samples are also under investigation.(33)

3.3 Post-polypectomy Surveillance

3.3.1 Principles of surveillance

In a broad sense, surveillance implies careful and systematic observation of something, for example camera surveillance in the streets or counting and registration the number of cases of a disease in a country. Medical surveillance can be applied to a specific disease, like influenza, where there typically is a continuous, passive surveillance to monitor changes, and – if needed – take necessary action (e.g. infectious disease control measures).(77, 78) On the other hand, surveillance can be applied to a person, which is observed closely over time to detect early signs of a disease in the individual, for example colorectal cancer surveillance in individuals with inflammatory bowel disease.(79)

3.3.2 Post-polypectomy surveillance recommendations

Studies have shown that certain polyp characteristics predict the risk of developing (metachronous) CRC.(12, 80) Polypectomy may be performed as part of screening (follow-up or primary colonoscopy), or colonoscopy due to other indications. Post-polypectomy surveillance after colonoscopy usually means the systematic and regular follow-up of individuals who, through characteristics of polyps removed at colonoscopy, have been identified as having high-risk of developing CRC.(81) These individuals are invited to repeated colonoscopies to detect CRC or new precursors of CRC at an early stage.(10) Of note, repeated FOBT in a CRC screening program is *not* surveillance by this definition because all tests are performed on average-risk individuals.

Recommended surveillance intervals are based on risk stratification, which again depend on the characteristics of polyps removed (i.e. number, size and histology) at the index colonoscopy before surveillance. Estimated 10 year risks of developing CRC after baseline colonoscopy are 0.5% and 1.4% for low- and high-risk individuals, respectively,(82-85) but the exact definition differs slightly between guidelines, and some guidelines also include recommendations for individuals at intermediate-risk.(81, 86, 87)

The recommended surveillance intervals are shorter in individuals with high-risk, compared to low-risk. Most international guidelines recommend post-polypectomy surveillance in high-risk individuals after three years, and low-risk individuals to return to screening (i.e. new screening test) 5 or 10 years later, depending on the screening guideline.(81, 86, 87) Shorter intervals between screening or surveillance procedures will increase colonoscopy service demand, and because all positive CRC screening tests (except primary colonoscopy screening) lead to a follow-up colonoscopy, both screening and surveillance demand facilities and personnel to perform colonoscopy. Not all individuals with polyps have higher risk of CRC, compared to the general population, and some may even have lower risk without need of surveillance.(88)

3.3.3 The European Polyp Surveillance trial (EPoS)

Surveillance recommendations after polyp removal are based on moderate or low quality evidence and have as of today not been investigated in a large-scale randomized clinical trial with long follow-up.(81, 86, 87, 89) The European Polyp Surveillance trials (EPoS) is a group of large multicenter trials in the European countries Austria, Denmark, Norway, Poland, Portugal, Spain, Sweden and

The Netherlands that investigate post-polypectomy surveillance in individuals with colorectal polyps.(89) The scope of this theses are EPoS trials I and II. Both trials are randomized parallel-group intervention trials comparing different surveillance intervals in individuals with low- or high-risk adenomas.(89) Trial inclusion was completed in 2020 and the primary endpoint is incidence of CRC after 10-years of follow-up, meaning that the final results will be available in 2030.

3.4 Quality and practice variability in gastrointestinal endoscopy

3.4.1 Health care quality

There are several ways to define quality in health care, one of which is the definition by The World Health Organization: "Quality of care is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes".(90) Important traits of good quality health care are that it is provided effectively and safely to the receiver. Other important traits are appropriate waiting time, efficient use of resources (avoid waste) and equal health care quality independent of personal characteristics such as ethnicity or gender.(91, 92)

3.4.2 Quality indicators

Health care quality should be continuously measured to help providers assess their own performance and detect areas for quality improvement.(90) Quality indicators are metrics to indirectly measure different aspects of health care quality in an institution, department or individual health care personnel. Quality indicators are also called "performance indicators" or "quality metrics".(93, 94) Examples are patient survival 30 days after hospital discharge or number of colon perforations following colonoscopy. The purposes of quality indicators are to:

- Reveal poor quality (e.g. in a hospital, a department or an individual physician) and support quality improvement
- Be open to the public about the quality of provided health care
- To compare health care quality, for example between institutions or physicians
- Choosing quality indicators is choosing what gets attention and prioritization (95)

Good quality indicators share some key characteristics (94, 96): First, quality indicators should measure something with clinical importance, for examples a disease with high prevalence or severe outcome, or high use of health care services. Second, the indicator should be clearly

defined and described, feasible to measure and with a known threshold for good health care quality. Third, the quality indicator should be sensitive to change, meaning that actions taken to improve quality of care (or changes leading to a reduction in quality of care) leads to a change in the measured value of the quality indicator. If the quality of care is unchanged, the measured value should also stay unchanged. Fourth, quality measures should be counted by someone else than the person (or other entity) that is being evaluated. Lastly, the measurement and monitoring of a quality indicator should not pull attention away from other, more relevant aspects of health care quality.

Ideally, quality indicators should be evidence based in that it should have a documented association to health care quality.(97) Such evidence may not be available for all quality indicators, for example due to practical or ethical hindrances to conduct a clinical trial investigating the question. Instead, some quality indicators are chosen based on experience and "common sense" judged by experts.(98)

Table 1: Categorization of quality indicators

Indicator	Description	Example
Structure	Measurements of the setting where health care is provided (infrastructure, equipment, personnel and their qualification, available guidelines, etc.)	Number of physicians in an emergency department
Process	Measure activities in the process of care ("the means to provide health care"); when and what was done for the patient and how well provision of health care was done.	Colonoscopy withdrawal time
Outcome	Measure of an outcome of care, meaning patient health status (e.g. mortality or patient disability) or events that follow care.	30-days mortality after hospitalization

There are several ways to categorize quality indicators, one of which relates to what the indicators measure: structure, process or outcome (Table 1).(91, 94) Some quality indicators are universal, while others may be specific for certain health care institutions (e.g. general practitioner office) or patient group (e.g. patients with myocardial infarction). Quality indicators may function as a sentinel that trigger action or further investigation if present/detected, or function as a continuous quantitative (rate-based) monitoring of the health care quality.

Outcome measures are the ultimate validators of the quality of care, but time from a change in practice to a measurable change in outcome may be long, even years.(99) Thus, other more short

term measurements are needed, such as the steps in patient care (i.e. process indicators) or short-term outcome quality indicators that allows for early detection of poor quality health care that should be acted upon.

3.4.3 Quality indicators in gastrointestinal endoscopy

Like many other health care services, there are recommended quality indicators in gastrointestinal endoscopy services.(39, 100, 101) Quality indicators in gastrointestinal endoscopy may be classified as pre-, intra- or post-procedure. Some recommendations are specific for colonoscopy.(39) Important quality indicators in colonoscopy include a valid indication for the procedure, adequate bowel preparation, withdrawal time, adenoma detection rate (ADR), frequency of post-procedure complications (e.g. perforation or post-polypectomy bleeding) and frequency with which patients follow recommended follow-up intervals (surveillance) after polyp- or cancer removal.(39)

Recommendations for quality indicators usually set a minimum and/or target (desired) standard – by some termed "benchmark" - of each quality indicator. For example, it is recommended that endoscopists achieve ≥25% ADR (i.e. proportion of patients with one or more adenoma(s) detected and removed) in average-risk individuals undergoing colonoscopy.(39, 101) The performance target may be specified further by patient population; for example target ADR of ≥20% in women and ≥30% in men, and cecum intubation rate of ≥95% in a screening population, compared to ≥90% overall. Furthermore, some guidelines specify the level of analyzing the quality indicator (e.g. at the endoscopy service or individual endoscopist level).(101)

There are quality indicators that are country specific. For example, in Norway, patients undergoing colonoscopy are not routinely sedated and thus do not need a documented sedation plan as recommended in American guidelines.(39, 102) Consequently, the Norwegian national registry of colonoscopy service performance (Gastronet) has the proportion of patients with severe pain during the procedure as one of its quality indicators.(103)

3.4.4 Quality assurance and unwanted variation

It is highly recommended to perform systematic training in colonoscopy to ensure high quality endoscopy service. Ideally, the supervision should be performed by trained endoscopists.(104)

Several studies have shown variation in gastrointestinal endoscopy performance, including primary colonoscopy screening.(48, 105) Such variation may be unwanted and available to quality improvement.

There are several ways to correct unwanted variation and poor performance and what method is best suited depend on the cause. For example, an endoscopist may have low ADR due to too short withdrawal time, meaning that the colon mucosa is not inspected thoroughly enough. Endoscopist training in what to look for (i.e. how to "use" the extra withdrawal time) can help improve ADR.(106) Alternatively, if a clinic experience a large number of patients coming for colonoscopy without having performed bowel preparation, the clinic should look at the information given to the patients before the procedure.(39, 101) The information may not clearly state that the patients need to perform bowel preparation beforehand, or there may be worthwhile to remind the patients the day before the procedure that they need to start bowel preparation.

4 Thesis aim

The aim of the thesis is to investigate comparative effectiveness and performance of colorectal cancer screening and gastrointestinal endoscopy service.

The thesis comprises of three papers, each with a research question based in the thesis aim:

- Paper 1: What are the long term effects of sigmoidoscopy screening, compared to usual care, on CRC incidence and mortality?
- Paper 2: Is there an additional benefit in effect of colonoscopy screening effect on CRC incidence and mortality?
- Paper 3: Is there variability in colonoscopy performance in polyp removal before surveillance?

5 Materials and methods

5.1 Paper 1

5.1.1 Participants and intervention

There are four randomized clinical trials comparing sigmoidoscopy screening to usual care (i.e. no screening invitation); three European and one in the United States.(53-56) The European trials are the Norwegian Colorectal Cancer Prevention trial (NORCCAP), UK Flexible Sigmoidoscopy Screening Trial (UKFSST) and Italian Screening for COlon and REctum trial (SCORE). The fourth trial is named U.S. Prostate-Lung-Colorectal-Ovarian cancer prevention trial (PLCO).

All four trials' characteristics are summarized in Table 2. PLCO, UKFSST and SCORE randomized participants based on their expressed interest to participate. Investigators in NORCCAP randomized from the population registry (pre-consent randomization, see 5.4.5), meaning that individuals in the usual care group were not informed of their participation. Detailed information about inclusion criteria can be found in each trial's original publications. (53-56) Of note, none of the trials included individuals with a known CRC history and three of the four trials did not include individuals with a recent investigation of the colon (e.g. colonoscopy).

Included individuals were, by randomization, assigned to either receive an invitation to screening by sigmoidoscopy, or no invitation (usual care). All trials' screening group participants were invited to once-only sigmoidoscopy screening, except PLCO where participants were invited to a second sigmoidoscopy procedure 3 or 5 years after the first invitation. Only PLCO participants who attended the first, baseline screening invitation were counted as screening attenders in Paper 1. In NORCCAP, 50% of individuals invited to sigmoidoscopy screening were also invited to deliver one stool sample for FIT-screening. Baseline screening was performed years 1993 to 2001. There were no organized CRC screening programs in any of the trial countries at trial initiation but a screening program was introduced in the U.K. (FOBT) and Italy (FIT) during follow-up. Our main analyses in Paper 1 included individuals screened between age 55 and 64 years because that age group were included in all trials.(53-56) Additionally, this is the age group that CRC screening recommendation recommend to start screening. Individuals aged 50-54 years in NORCCAP and 65-74 in PLCO were included in sensitivity analyses.

Table 2: Characteristics of randomized sigmoidoscopy screening trials.

	NORCCAP		PLCO	UKFSST	SCORE
Country	Norway		United States	United Kingdom	Italy
Participant identification, consent procedure	Pre-consent randomization		Expression of interest before randomization	Expression of interest before randomization	Expression of interest before randomization
Intervention (screening group)	Once-only invitation to sigmoidoscopy screening. Half of participants randomized to the screening group were further randomized (1:1) to an invitation to provide a stool sample for fecal occult blood testing.		Invitation to sigmoidoscopy screening (at baseline), and a second invitation to screening 3 or 5 years later	Once-only invitation to sigmoidoscopy screening	Once-only invitation to sigmoidoscopy screening
Participant age at enrolment, years	50-54	55-64	55-74	55-64	55-64
Randomization ratio (screen:usual care)	1:5.4	1:3	1:1	1:2	1:1
Inclusion period	2001	1999-2000	1993-2001	1994-1999	1995-1999

Participants in the usual care (control) group did not receive any screening invitation. There were no organized CRC screening during the trials' inclusion period. There were some opportunistic screening in the United States and Italy, but little opportunistic screening in Norway and the United Kingdom. *(Adapted from Table 1 in paper 1)*

5.1.2 Data acquisition

Investigators of the four trials shared data on number of individuals at risk, number of CRC cases (overall, proximal and distal CRC) and deaths (all-cause or by CRC), by sex, randomization group and 5-year age group. The proximal colon was defined as the splenic flexure, transverse colon, hepatic flexure, ascending colon and the caecum (including the appendix). The distal colon was defined as the rectum, sigmoid colon and descending colon.

Data was aggregated into 1-year periods for NORCCAP, PLCO and SCORE, and, due to restrictions in data sharing, 3-year periods for UKFSST. Shared data corresponded to the data used in the individual trials' latest publications but in UKFSST, events after 15-years of follow-up were aggregated into "≥ 16 years follow-up". Small UKFSST data cells with less than 8 events/individuals were set to 7 in our analyses. Furthermore, CRC deaths by cancer site was not available from UKFSST due to several data cells with low number of events within the 3-year intervals.

5.1.3 Statistical analyses

Our study outcomes were CRC incidence and mortality, overall and by predefined subgroups: sex, age group (55-59 years and 60-64 years) and cancer site (distal colon and proximal colon). In addition, we wanted to look at the all-cause mortality. All analyses were intention-to-treat comparison of the screening group and usual care group. We limited the follow-up to 15-years as this was the minimum follow-up time in all trials.

Because we had detailed data from all four trials, we wanted to pool each variable (i.e. no trial weighting) to perform the analysis as though the data were from a single trial. However, while PLCO and SCORE had a 1:1 ratio between screening and usual care groups, NORCCAP (age group 55-64) and UKFSST had a 1:3 and 1:2 screening versus usual care ratio, respectively. Since it was unlikely that the CRC incidence and mortality were similar in all included trial populations, then pooling the data from trials with different randomization ratios would lead to biased results. If, for instance the colorectal cancer risk was higher in Norway than the other three included countries, and the Norwegian trial had a 1:3 randomization ratio, then the pooled colorectal cancer risk would be lower in the screening group than in the usual care group – even in the absence of sigmoidoscopy screening. Therefore, the number of individuals in the usual

care group in the two trials were reduced to the same number as the screening group in the same trial (i.e. 1:1 ratio). Number of events (CRC cases and deaths) were reduced by the same proportion as the number of individuals.

Next, we calculate yearly and cumulative CRC incidence, CRC mortality and all-cause mortality rates overall in screening and usual care groups, using a Poisson model. Rates were used to calculate incidence rate ratios (IRR), mortality rate ratios (MRR) and rate differences per 100 individuals (over 15 years). Calculations were repeated by sex, age group and CRC location (proximal or distal). CRC mortality by location were without UKFSST data (see 5.1.2).

An alternative approach to our pooling method is a meta-analysis, which we performed in a sensitivity analysis using a random effect model. In another sensitivity analysis we removed individual trials to look for substantial changes in analysis results. Tests were two-sided with a significance level (p-values) of 0.05. We used Stata 17.0 (StataCorp, College Station, TX, USA) for all analyses.

5.2 Paper 2

5.2.1 Participants and intervention

In recent years, sigmoidoscopy screening is switched to primary colonoscopy screening across the world due to the assumption of a better colonoscopy screening effect in the proximal colon. The only published randomized colonoscopy screening trial have limited follow-up (10 years), and did not report colonoscopy effectiveness by location (proximal or distal colon) or sex.(64) Furthermore, overall effectiveness on CRC incidence was similar to that of sigmoidoscopy screening trials.(64, 107-110) In Paper 2, we wanted to simulate primary colonoscopy screening to estimate the long-term effects of colonoscopy screening, compared to usual care or sigmoidoscopy screening. Similar to Paper 1, we took advantage of detailed data from the four existing randomized sigmoidoscopy screening trials, to make our colonoscopy screening estimates.

In other words, study population in Paper 2 was similar to Paper 1, but with some important differences. First, in Paper 2, we used cumulative data from the total follow-up time from each

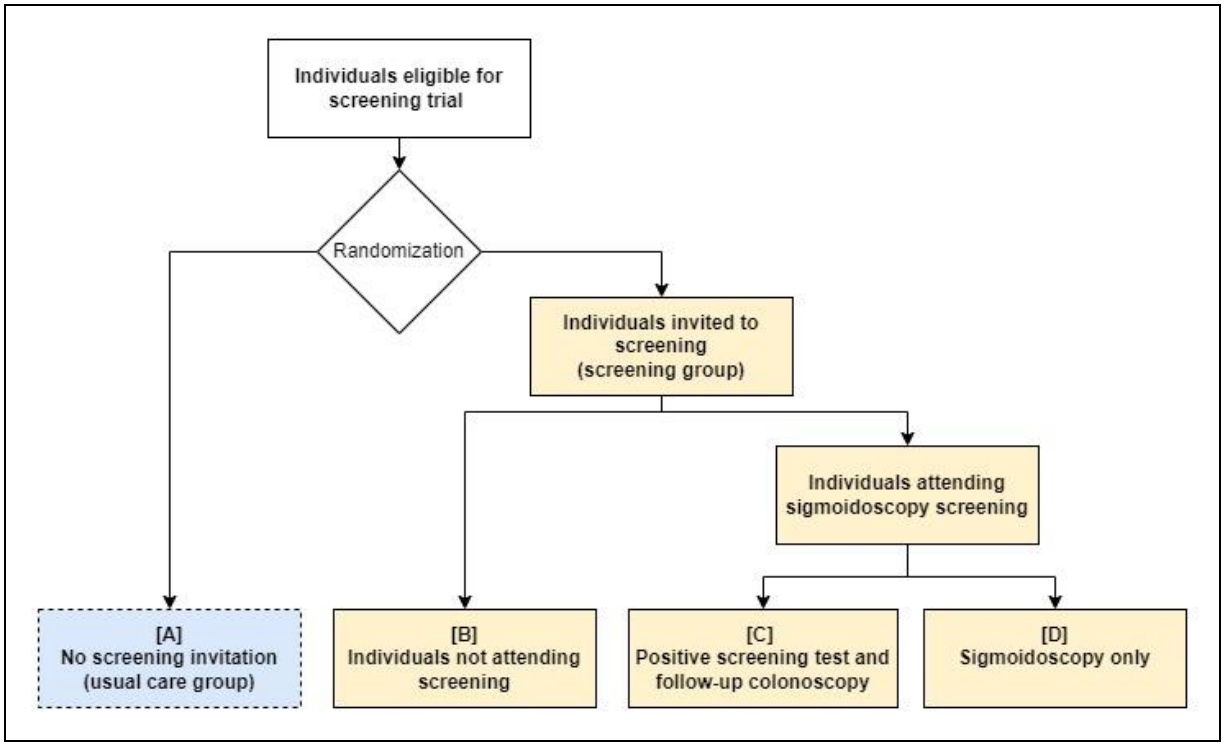
trial, which ranged from 15 to 17 years for incidence and 15 to 19 years for mortality.(53-56) This meant that we could share and receive data on the exact number of individuals, person-years at risk, CRC cases (overall, and by site; proximal and distal colon), CRC death (overall, and by site; proximal and distal colon), and all-cause deaths.

Second, participants who attended the 3 or 5 year screening only (not baseline screening) were counted as screening attenders. Third, in addition to data on individuals randomized to usual care, we acquired data on sigmoidoscopy screening attendance and number of individuals attending colonoscopy after a positive screening sigmoidoscopy, according to the trial definition of a positive screening test.(53-56) Data was used to separate the screening group into three groups, based on screening attendance and whether the sigmoidoscopy screening test was followed by a colonoscopy or not. Thus, there were four groups included in the simulation model (Figure 2):

- Group [A] Individuals without screening invitation
- Group [B] Invited individuals who did not attend screening
- Group [C] Sigmoidoscopy screening attenders with a positive screening test, and who attended a subsequent colonoscopy
- Group [D] Sigmoidoscopy screening attenders with a negative screening test, or who had a positive sigmoidoscopy screening test but did not attend follow-up colonoscopy

We wanted to validate our colonoscopy simulation to the recent results from the NordICC trial.(64) We chose to use 10 year follow-up data from NORCAPP and data from the Norwegian portion of NordICC because these were most comparable in terms of participant risk factors (same country, participant age and health care system), both used pre-consent randomization and had comparable screening attendance rates: 65% in NORCCAP (sigmoidoscopy) and 61% in NordICC (colonoscopy, Norwegian portion).

Figure 2: Flow chart of simulation model groups, based on colorectal cancer screening trial randomization, screening attendance and follow-up. Blue box with dashed outer line are individuals randomized to the usual care group, and yellow boxes with solid outer lines are individuals randomized to the screening group.



5.2.2 Colonoscopy screening simulation

Our assumptions were:

I. Attendance to colonoscopy screening is the same as the observed attendance in the sigmoidoscopy screening trials.

II. The effect of colonoscopy screening is the same as the effect of colonoscopy after a positive sigmoidoscopy observed in the trials (Figure 2, group [C]).

III. The reduction in distal CRC incidence and mortality is the same after colonoscopy screening as the reduction observed after sigmoidoscopy screening in the trials (Figure 2, group [D]).

IV. The relative reduction in proximal CRC incidence and mortality after colonoscopy screening is the same as the relative reduction in distal CRC incidence and mortality observed in the sigmoidoscopy screening trials.

Sigmoidoscopy screening effect

Based on our assumptions, we estimated the long-term (15 years or more) effectiveness of primary. Calculations were performed through several steps. First, to apply assumption IV, we needed to estimate the long-term effects of sigmoidoscopy screening in the distal colon. We used the observed data from each sigmoidoscopy screening trial to calculate the cumulative CRC incidence and mortality rates in screening and usual care groups, overall and by site (proximal and distal colon). Next, we used the rates to calculate cumulative CRC incidence and mortality rate ratios and rate differences (i.e. CRC cases and CRC deaths prevented per 100 000 person-years [PYr]) in each trial, comparing screening versus usual care group:

$$Rate\ ratio_{Sigmoidoscopy} = \frac{\frac{Events_{Screening\ group}}{PYr_{Screening\ group}}}{\frac{Events_{Usual\ care\ group}}{PYr_{Usual\ care\ group}}}$$

$$Rate\ difference_{Sigmoidoscopy} = \frac{Events_{Screening\ group}}{PYr_{Screening\ group}} - \frac{Events_{Usual\ care\ group}}{PYr_{Usual\ care\ group}}$$

We then pooled the trial results using a traditional meta-analysis approach, meaning that trials were weighted using the inverse-variance of the trial specific estimates as weights, to calculate cumulative CRC incidence and mortality rate ratios and rate differences across trials.

Additionally, we calculated CRC and CRC death risks by dividing the number of events by the number of individuals at risk (instead of person-years as was used for the rates), followed by calculation of the risk differences. Risk difference was used to calculate the number needed to screen (NNS) by sigmoidoscopy to prevent one CRC case or CRC death. NNS was calculated as the inverse of the risk difference across trials.

Colonoscopy screening effect

We now had the numbers needed to perform our colonoscopy screening simulation to estimate the effectiveness of colonoscopy screening, and to compare the results to no screening (usual care group) and sigmoidoscopy screening. From each sigmoidoscopy screening trial, we identified rate ratios for distal CRC incidence and mortality, and the number of events (CRC cases and CRC deaths) in the proximal colon among sigmoidoscopy screening attenders without subsequent colonoscopy (i.e. screening negative; Figure 2, group [D]). Number of events were

then multiplied with one minus the rate ratio, to estimate the additional number of events prevented by colonoscopy screening (compared to sigmoidoscopy screening):

$$Events\ prevented\ proximal\ colon_{Colonoscopy,\ \ screening\ negative} = Events\ proximal\ colon_{Sigmoidoscopy,\ \ screening\ negative} * (1 - Rate\ ratio_{Sigmoidoscopy\ distal\ colon})$$

The next step was to calculate the trial specific and overall effects of colonoscopy screening on CRC incidence and mortality. Number of events in each trial were calculated by subtracting the number of events prevented, from the number of proximal events in the screening groups:

$$Events\ proximal\ colon_{Colonoscopy,screening\ group} = Events\ proximal\ colon_{\ Sigmoidoscopy,screening\ group} - Events\ prevented\ proximal\ colon_{Colonoscopy,screening\ negative}$$

We used the resulting number of events in the colonoscopy screening group to calculate cumulative rates, rate ratios and rate differences in each trial, comparing colonoscopy screening to usual care. Similar to the sigmoidoscopy screening trial calculations, we used a meta-analysis approach to calculate cumulative incidence and mortality rate ratios and rate differences per 100 000 person-years (colonoscopy screening compared to usual care) across trials. Risk and risk differences were calculated to estimate NNS by colonoscopy compared to usual care. Bootstrapping was used to estimate the variance of the colonoscopy metrics.

Our final comparison was between sigmoidoscopy screening and colonoscopy screening. Comparisons were calculated and presented as rate ratios, rate differences (additional events prevented per 100 000 person-years) and numbers needed to switch (i.e. number needed to switch from sigmoidoscopy screening to colonoscopy screening, to prevent one additional event), calculated as the inverse of the risk difference between risks in sigmoidoscopy screening and colonoscopy screening groups:

$$Numbers\ needed\ to\ switch = \frac{1}{Event\ Risk_{sigmoidoscopy\ screening} - \ Event\ Risk_{colonoscopy\ screening}}$$

All analyses (sigmoidoscopy and colonoscopy screening effects) were repeated for women and men separately.

Simulation model validation

To evaluate the validity of our colonoscopy screening simulation, we applied the same analytical steps as previously described (but per 10 000 individuals instead of 100 000 person-years to make results comparable to the NordICC trial (64)), on the 10-year follow-up data on CRC incidence in the Norwegian sigmoidoscopy trial (NORCCAP trial (55)). The resulting estimates and confidence intervals were compared to the observed results from the Norwegian portion of the NordICC trial. A similar comparison for CRC mortality was not performed because these results were not available by country in the NordICC trial.

5.3 Paper 3

5.3.1 Background

Colonoscopy is the cornerstone of all CRC screening strategies and diagnostics of gastrointestinal symptoms. The quality of the colonoscopy procedure is key to the effectiveness of screening (assessed in Paper 1 and 2) and a high-quality procedure is a prerequisite for the patient to enter post-polypectomy surveillance. In Paper 3 we wanted to look at the quality of the endoscopic procedure at baseline, meaning before the start of surveillance. Both repeated procedures and colonoscopy surveillance put extra demand on endoscopy resources and should preferably be kept at a minimum. Ideally, most individuals should only need one endoscopy before surveillance start, but it is unknown how many patients need to undergo several procedures to remove all detected polyps.

The recent completion of participant inclusion to the EPoS I and II trials provided an excellent opportunity to look at potential variability in colonoscopy quality across countries, endoscopy center and endoscopists. Further, we were able to widen the scope and looked at quality of colonoscopies following other indications than screening (e.g. positive FIT test or symptoms).

5.3.2 Participants

Eligible participants were individuals aged 40 to 74 years with polyps removed (i.e. “clean colon”) after a high-quality colonoscopy with polyp removal, meaning that the patient was

entering post-polypectomy surveillance. Individuals with zero or more than ten adenomas were not invited to the trial. Patients with known history of colon surgery, inflammatory bowel disease, history of CRC or hereditary cancer syndrome (e.g. Lynch syndrome), ongoing cancer treatment, severe comorbidity (New York Hears Association score 3 or 4) or need of nursing services over a longer period of time were excluded from the trial. If more than one colonoscopy was needed to achieve clean colon, all colonoscopies (i.e. baseline colonoscopies) had to be performed within 52 weeks for the individual to be eligible for participation. Patients were not excluded based on the indication of the initial colonoscopy, meaning that both asymptomatic (i.e. screening) and symptomatic individuals were included in the trial.(89)

Eligible patients were stratified into low- or high-risk for developing CRC, based on the individual's adenoma characteristics (e.g. histology findings) at baseline. Based on the risk stratification, patients were included in either of the two trials and each trial randomized participants to different surveillance intervals:

- In EPoS I, patients with low-risk adenomas (one or two <10 mm adenomas with tubular histology and low grade dysplasia) were randomized to surveillance after 5 and 10 years OR after 10 years only.
- In EPoS II, patients with high-risk adenomas (three to ten adenomas, adenoma(s) ≥10 mm in diameter, adenoma(s) with villous growth pattern or high-grade dysplasia) were randomized to surveillance after 3, 5 and 10 years OR after 5 and 10 years.

5.3.3 Data acquisition

We acquired data on all patients included in the EPoS I and II trials in Denmark, Norway, Poland, Spain, Sweden and The Netherlands. Austria and Portugal were not included in our analysis due to low number of enrolled patients. Initial indication for colonoscopy were categorized as primary colonoscopy screening, colonoscopy following a positive FIT, colonoscopy because of symptoms and colonoscopy because of other indications (e.g. family history of CRC). Due to the strict eligibility criteria, participants within each trial shared risk factors, which made them comparable even though the initial indication differed. Data on age and sex were available for all trial participants

For each baseline colonoscopy we acquired characteristics of removed polyps (e.g. number, size and histology), BBPS, and cecum intubation (yes/no). In patients with repeated colonoscopy, we acquired the endoscopists' reason to repeat the procedure (the case report form only allowed one reason): poor bowel cleansing; anticoagulant or antiplatelet therapy, incomplete colonoscopy, piecemeal polyp resection (e.g. to assess a polypectomy scar), polyps left in situ, incomplete polypectomy or unspecified reason.

All patients from the Netherlands and patients in Poland with polyps 20 mm or larger were excluded from analysis due to local procedure policies; Dutch patients with two or more colonoscopies were not included in any of the EPoS trials and all Polish patients with large polyps (20 mm or larger) were scheduled for a repeated colonoscopy. Inclusion of these data would bias the observed proportion of patients with two or more colonoscopies resulting in a lower (zero) proportion in the Dutch data and higher proportion in the Polish data. Patients referred to colonoscopy following positive findings at screening sigmoidoscopy (performed at two Norwegian sites) were also excluded because polyps could have been removed at the sigmoidoscopy procedure.

5.3.4 Outcome variables and analysis

Because of shared clinical characteristics, it should be possible to achieve high-quality colonoscopy assessment of the colon at the first procedure for the majority of patients. Thus, we dichotomized patients into two groups based on the number of colonoscopies needed to enter surveillance;

1. Patients in need of 1 colonoscopy
2. Patients in need of ≥2 colonoscopies

Our primary outcome was the proportion of patients in need of repeated (2 or more) colonoscopies to achieve a colon without polyps – that is, before trial inclusion. Each trial was analyzed separately and results were presented by country, endoscopy center, and individual endoscopists. Our analysis on individual endoscopists was limited to endoscopists who enrolled 30 or more patients to the trial (counted separately for EPoS I and II).

Age was presented as median. Other continuous variables were categorized into groups: number of polyps: 1-2, 3-4 or ≥5; size of largest polyp: <10 mm, 10-19 mm or ≥20 mm; number of adenomas: 1-2, 3-4 or ≥5; size of largest adenoma: <10 mm, 10-19 mm or ≥20 mm. These and other categorical variables were presented as absolute numbers with percentage. For the proportion of repeat baseline colonoscopy, we calculated 95% confidence intervals using an exact binomial approach (Clopper-Pearson).(111) The approach is conservative (wide CI), especially when proportions are close to 0 or 1. As in Paper 1 and 2, we used Stata 17.0 (StataCorp, College Station, TX, USA) to create figures and perform calculations. R studio (version 2022.2.3.492. R Studio, PBC, Boston, MA) was used to calculate confidence intervals and make tables.

5.4 Ethical considerations

5.4.1 Ethical board approvals and trial registration

The individual sigmoidoscopy trials (e.g. NORCCAP) and the EPoS project were approved by local ethical boards. All trials were registered before patient enrollment (NORCCAP: ClinicalTrials.gov NCT00119912; PLCO: ClinicalTrials.gov NCT01696981; UKFSST: ISRCTN number 28352761; SCORe: ISRCTN number 27814061; NordICC: ClinicalTrials.gov NCT00883792; EPoS project ClinicalTrials.gov NCT02319928).

5.4.2 Funding

I received personal fees from South Eastern Norway Health Trust as a PhD research fellow to conduct the work resulting in the three papers in the current thesis. The three papers were also funded by the Research Council of Norway. All trials were sponsored by research grants in the trials' respective countries and run by investigators employed in academic or governmental institutions. The trial sponsors had no influence on the study design, data collection or analysis, data interpretation, or writing or publication of the results. Funding sources for each trial are listed below:

The NORCCAP trial received funding from the Norwegian government and Norwegian Cancer Society. The PLCO trial received funding from the National Cancer Institute in the United States.

The UKFSST has received funding from the UK Medical Research Council (MRC) and the National Institute for Health Research (NIHR), under the MRC-NIHR Efficacy and Mechanism Evaluation (EME) Programme (reference 09/800/08), and the NIHR Health Technology Assessment (HTA) Programme (reference 16/65/01). The work of the Cancer Screening and Prevention Research Group (CSPRG) is also supported by a Cancer Research UK Prevention and Population Research Committee Programme Award (reference C53889/A25004). The SCORE trial has received funding from the Italian Association for Cancer Research, Italian National Research Council, Istituto Oncologico Romagnolo, Fondo "E. Tempia," University of Milan, and Local Health Unit ASL-Torino.

The NordICC trial was supported by research grants from the Nordic Cancer Union, Norwegian Cancer Society, Research Council of Norway (197309), and Health Fund of South-East Norway (5135); bowel preparation free of charge for colonoscopies in Norway from Dr. Falk Pharma; grants from the National Center for Research and Development of Poland (N R13 0024 04), Polish–Norwegian Research Program (PolNor/204233/30/2013), Medical Center for Postgraduate Education (501-1-09-12-12/22), the Polish Foundation of Gastroenterology, the Dutch Ministry of Health and Health Care Prevention, Program–Implementation (ZonMw 2008), the Netherlands Organization for Health Research and Development of the Dutch Ministry of Health (ZonMw 120720012), the Center for Translational Molecular Medicine (CTMM DeCoDe-project), and the Swedish Cancer Foundation (2010/345 and CAN 2013/553); a Distinguished Professor Award from the Karolinska Institutet, Regional forskningsfond i Uppsala– Örebro regionen (2368/10-221, to Dr. Adami); and a grant from Afa (130072).

The EPoS trials were funded by research grants from the European Union (102012); Norwegian Research Council (102346); Regional Health Trust of South-East Norway (39692); Danish Cancer Society (R167 - A11048); Instituto de Salud Carlos (III) Madrid, Spain (PI17/00837 and PI21/01771); Dutch Cancer Society (10274).

5.4.3 Principle of equipoise

Clinical research involving human subjects poses ethical challenges. Participants risk their own health to test new treatment options, which can cause harm or even death. It is only ethical to conduct clinical trials if there is clinical equipoise, meaning that there is actual uncertainty to

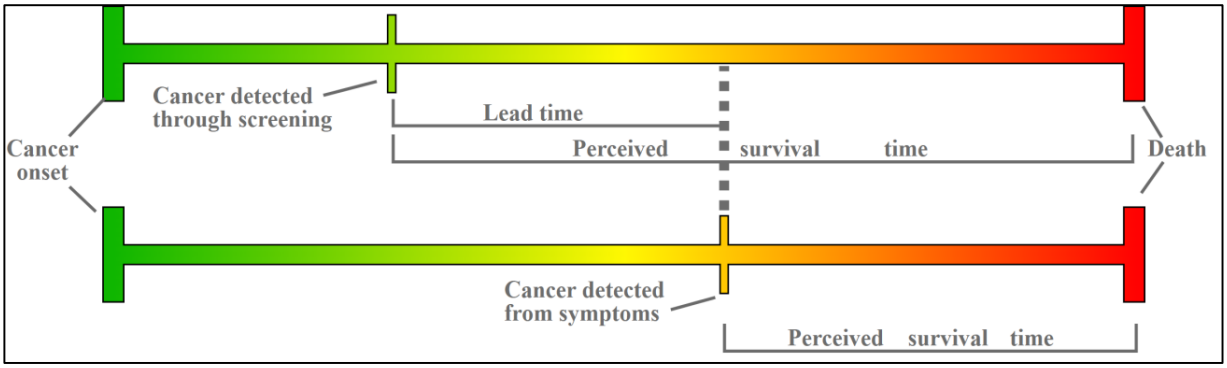
whether the intervention under investigation is beneficial or not.(112) To conduct a clinical trial on an intervention that is already known to be inferior would leave participants from superior, (more) effective, treatment options, or, if no effective treatment is available, only put the participants at risk of harms from the (ineffective) intervention. Whether an intervention is beneficial depends not only on positive merits (e.g. reduced mortality), but also on the intervention's burdens and harms (e.g. quality of life, financial costs).

Some trials involve patients with severe disease with few or no treatment options. Here, many of the participants may benefit from the intervention, if it proves to be an effective treatment. It has been argued that clinical trials involving placebo is only ethical when no treatment option exists.(112)

5.4.4 Ethics of screening

Cancer screening trials in average-risk populations differ from trials on individuals with a disease because most participants don't have and will never develop cancer. This majority that do not benefit from the intervention (screening) are still exposed to the burdens and harms of the screening intervention. In addition, early-detected cancer turn screening participants into patients at an earlier point in time than without screening.(29) If early detection does not change the course of the disease, early detection will even extend the individual's time as a patient due to lead time (Figure 3). As a result, survival time may increase even though mortality is unchanged due to the phenomenon caller lead-time bias.(29)

Figure 3: A diagram explaining lead time bias for cancer diagnosis. *(Figure made by Mcstrother [4 July 2011], Wikimedia Commons. Used under Creative Commons Attribution 3.0 Unported license.)*



Independent of screening method, screening involves a risk of false test results. A false positive test may not only involve risk related to follow-up procedures (e.g. colonoscopy) but can also lead to negative psychological effects on the individual. On the other hand, a false negative test may result in (false) reassurance for the patient, followed by a ”patient-delay” in contacting a physician when symptoms of CRC later start to develop.(113, 114)

These and other ethical issues with cancer screening (e.g. overdiagnosis, medicalization and fear of cancer in the target population, and length-time bias) are discussed more thoroughly in the scientific literature (115-120). Overdiagnosis and overtreatment are discussed later in the thesis (see 7.1).

5.4.5 Informed consent and randomization

The principle of informed consent and voluntary participation is important elements of clinical research. To be informed, eligible individuals need to understand potential benefits and harms of being a participant. Of note, people tend to be poor at evaluating risks and in general weight harms more than benefits (loss aversion).(121) Some potential harms (e.g. death) are concrete and relatively easy to explain to the patient/individual, while others (e.g. overdiagnosis) are harder to comprehend and convey to patient and/or trial participant. Indeed, a substantial proportion of participants in clinical trials have limited understanding of what they have consented to.(122)

All participants in EPoS and three of the screening trials (PLCO, UKFSST and SCORE) provided informed consent before randomization.(53, 54, 56, 89) NORCCAP differed from the other trials in that randomization was performed before acquiring consent – an approach termed pre-consent randomization.(123) Specifically, participants in NORCCAP were identified through a population registry and then randomized to either screening or no-screening (usual care). Only individuals randomized to screening were sent an invitation to participate in the trial. Similar to the other sigmoidoscopy screening trials, invited individuals needed to sign informed consent before undergoing any intervention (i.e. sigmoidoscopy), but individuals randomized to usual care were never informed of their participation. Outcome data on all randomized individuals were obtained from national registries, including individuals randomized to usual care and screening invited individuals who did not attend.(124)

The pre-consent procedure was approved by the Regional Ethics Committee (ID: 2010/3087) and we believe the pre-consent procedure can be ethically justified by several reasons:

A. Individuals in the usual care group receive the same health care as if they were not included. Thus, no extra burden or harm (e.g. due to trial intervention) are inflicted on them.
B. Data on cancer incidence and mortality are registered regardless of the trial. In fact, registration is mandatory according to Norwegian law.(125) In other words, the approach is similar to pure observational studies based on public registry data.
C. The gained knowledge by conducting the trial entails clear benefits for the society.

In addition, informing all usual care individuals about the trial would mean additional burdens and costs for the trial, and potentially raise anxiety among the individuals receiving information about their usual care group participation.(126)

Scientifically, the two approaches give answer to two slightly different questions, namely (A) to estimate the effect of offering an intervention (screening) to a population, and (B) to estimate the effect of the intervention itself, specifically sigmoidoscopy screening in Paper 1 and colonoscopy screening in Paper 2.(123, 127) Pre-consent randomization answers question (A), while post-randomization consent is better at answering question (B). The effect of offering screening to a population includes the effect of the intervention itself, but is also influenced by factors such as attendance rate and contamination in the no-screening group. This is discussed further later in the thesis (see 8.3, 8.4 and 8.6.4).

5.4.6 Data handling

Data on individuals from the national registries could be exposed when using them in a trial like the sigmoidoscopy screening trials, for example due to hackers accessing the database or researchers passing on the information by accident. To minimize the risk, data were gathered, analyzed and published on an aggregated level, where no individuals could be identified. Additionally, all data handling was performed within trial databases with enhanced security.

6 Summary of paper findings

6.1 Paper 1

15-Year Benefits of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality: A Pooled Analysis of Randomized Trials Ann Intern Med.2022;175:1525-1533. [Epub 11 October 2022]. Doi:10.7326/M22-0835

6.1.1 Baseline characteristics

The four trials included 358 204 individuals, of which 137 493 individuals were randomized to screening and 220 711 individuals were randomized to usual care. Screening attendance among those randomized to be invited to screening varied between the trials – from 58% to 84% (Table 3). Proportion of screened individuals who were referred to and attended colonoscopy also varied – from 13.7% (NORCCAP), down to 3.6% (UKFSST).

Table 3: Attendance rate and screening detected CRC in the randomized sigmoidoscopy screening trials included in Paper 1. Numbers are for individuals aged 55 to 64 years at screening. All numbers are proportions of individuals invited to screening (i.e. screening group). *(Adapted from Table 1 in Paper 1)*

	NORCCAP*	PLCO**	UKFSST	SCORE
Attendance, sigmoidoscopy screening	65%	84%	71%	58%
Women	67%	82%	69%	54%
Men	63%	86%	73%	61%
Attendance, follow-up colonoscopy	14%	14%	3.6%	4.5%
Screening detected CRC	0.2%	0.2%	0.3%	0.3%

** Not comparable to the other trials because NORCCAP was the only study pre-consent randomization (see 5.4.4).*

*** Not including participants who only attended the second sigmoidoscopy screening offered in the PLCO trial 3 or 5 years after the baseline invitation.*

6.1.2 CRC incidence

After fifteen years of follow-up, we found a pooled cumulative incidence of CRC of 1.84 cases per 100 individuals (95% CI: 1.77-1.92 cases) in the screening group and 2.35 cases per 100 individuals (95% CI: 2.27-2.44 cases) in the usual care group (rate difference: 0.51 cases per 100 individuals, 95% CI: 0.40 to 0.63 cases) (Figure 4, left). The CRC incidence reduction by sigmoidoscopy screening, compared to usual care, was thus 21% (IRR: 0.79, 95% CI: 0.75-0.83). Results were similar across age groups ($P_{\text{Chi-squared test}} = 0.169$). Results by site showed that the reduction was due to a reduction in distal CRC incidence (IRR: 0.68, 95% CI: 0.63-0.73), while there was no difference in proximal CRC incidence (IRR: 0.94, 95% CI: 0.87-1.03). Yearly CRC

incidence was consistently lower in screening group, compared to usual care group, except the first year due to screening detected CRC (Figure 5, top).

The absolute reduction in CRC incidence was greater in men (rate difference: 0.75 cases per 100 individuals, 95% CI: 0.56-0.93), compared to women (rate difference: 0.29 cases per 100 individuals, 95% CI: 0.15-0.44). In relative terms, this corresponds to a 25% reduction in men and 16% reduction in women. The sex difference in effect on CRC incidence was statistical significant ($P_{\text{Chi-squared test}} = 0.032$).

In men, the screening effect was similar among older (60-64 years) and younger (55-59 years) individuals, but in women the effect was lower and not statistical significant in older individuals, compared to younger individuals.

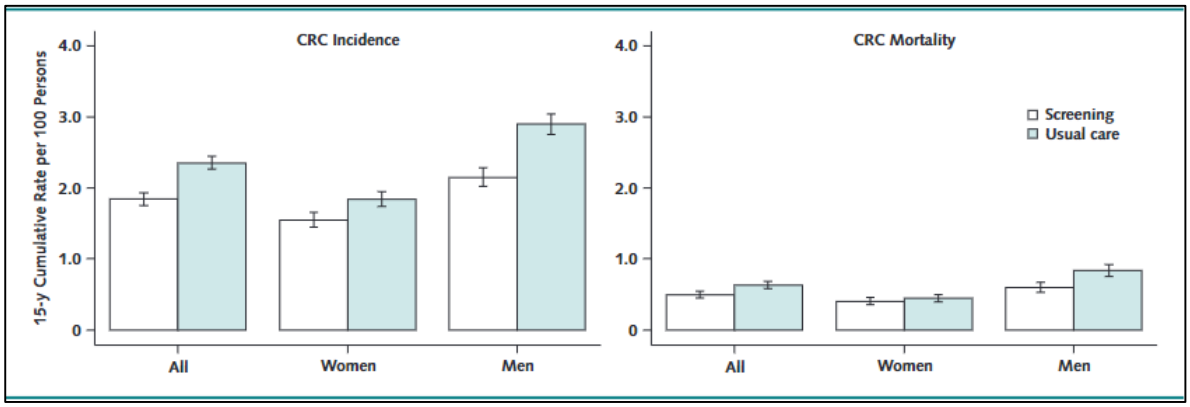
6.1.3 CRC and all-cause mortality

Cumulative CRC mortality after 15-years follow-up were 0.51 deaths per 100 individuals (95% CI: 0.48-0.56 deaths) among individuals invited to screening and 0.65 deaths per 100 individuals (95% CI: 0.61-0.70 deaths) among individuals not invited to screening (usual care group) (Figure 4, right). This means that, compared to usual care, invitation to sigmoidoscopy screening reduced CRC mortality by 0.13 deaths per 100 individuals (95% CI: 0.07 to 0.19 deaths) - corresponding to a relative difference of 20% (MRR 0.80, 95% CI: 0.72-0.88). As for CRC incidence, a reduction in CRC mortality was seen in the distal colon only (MRR 0.74, 95% CI: 0.61-0.90), and not in the proximal colon.

Yearly CRC MRR was close to one throughout the follow-up period, except years 10-12, when CRC mortality was lower in screening group individuals (Figure 5, bottom). MRR patterns were similar in women and men but, in general, estimates were closer to one in women.

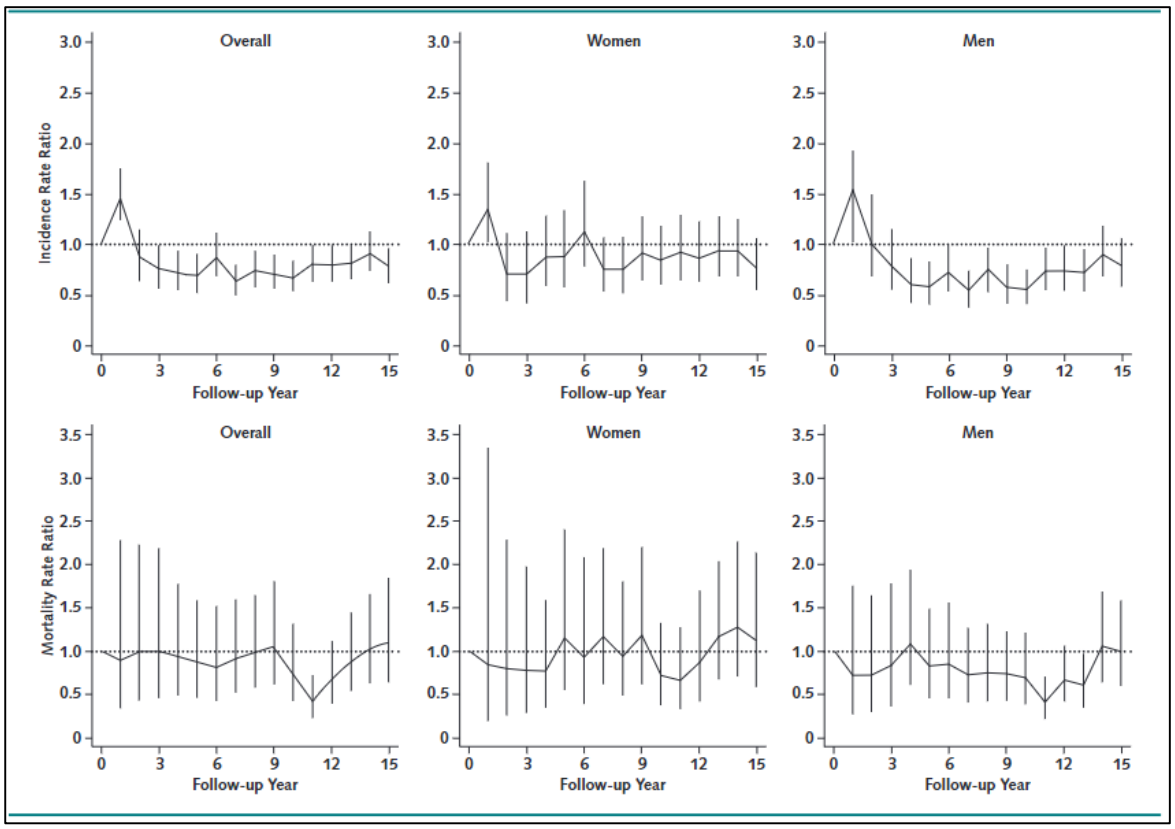
Sigmoidoscopy screening did not reduce CRC mortality in women (MRR 0.91, 95% CI: 0.77-1.17), independent of age, while a statistical significant reduction in CRC mortality was seen in men, overall (MRR 0.73, 95% CI: 0.64-0.83) and by age group. The sex difference in effect on CRC mortality was statistical significant ($P_{\text{Chi-squared test}} = 0.025$).

Figure 4: Pooled 15-year cumulative incidence rates (left) and cumulative mortality rates (right) of CRC per 100 persons (individuals) after sigmoidoscopy screening for all participants combined and for women and men separately.



Age at enrollment was 55 to 64 years. White bars represent persons randomly assigned to screening, and green bars represent those randomly assigned to usual care. Black whiskers represent 95% confidence intervals. *CRC= colorectal cancer. (Facsimile of figure 1 in Paper 1)*

Figure 5: Yearly rate ratios in incidence (top) and mortality (bottom) for CRC, by year since sigmoidoscopy screening, for all participants combined and for women and men separately.



Age at enrollment was 55 to 64 years. Dotted horizontal lines indicate no difference between participants in screening and usual care groups. Gray vertical lines represent 95% confidence intervals of yearly estimated incidence and mortality rate ratios. *CRC= colorectal cancer. (Facsimile of figure 3 in Paper 1)*

All-cause mortality was reduced by 2% in the screening group, compared to usual care group (MRR 0.98, 95% CI: 0.95-1.00, p-value = 0.016). Further, our results revealed a statistical significant reduction in all-cause mortality in men, but not in women: $MRR_{\text{all-cause women}}$: 0.98 (95% CI: 0.96-1.01), $MRR_{\text{all-cause men}}$: 0.97 (95% CI: 0.94-1.00).

6.1.4 Sensitivity analysis

The sigmoidoscopy screening effect on CRC incidence in women aged 60-64 years became statistically significant when we performed analysis without the PLCO-trial ($IRR_{\text{women 60-64 years, without PLCO}}$: 0.84, 95% CI: 0.74-0.97). The removal of other trials or inclusion of other age groups (50-54 years from NORCCAP or 65-74 years from PLCO) did not change our results.

We got similar results when using a meta-analysis approach instead of the pooling method (with 1:1 randomization ratio) that was used in our main analyses.

6.2 Paper 2

15-year Effectiveness of Colonoscopy Screening on Colorectal Cancer Incidence and Mortality - Simulation Analysis of Four Sigmoidoscopy Trials. Manuscript in review, December 2022.

6.2.1 Baseline characteristics

Similar to Paper 1, Paper 2 included 358 204 individuals aged 55-64 years, 181 971women (50.8%) and 176 233 men (49.2%). Screening attendance rate in each trial was slightly lower in women (54% to 85%) than in men (62% to 89%). The proportion of individuals invited to sigmoidoscopy screening who had a positive test and who later underwent follow-up colonoscopy also differed by trial and sex; from 2% in women and 5% in men in the UKFSST trial, to 18% in women and 28% in men in the PLCO trial.

6.2.2 Colonoscopy screening benefits on CRC incidence

If colonoscopy screening was performed, 50 (95% CI: 42-58) CRC cases per 100 000 person-years would be prevented, compared to no screening, which means a 30% reduction in CRC incidence (rate ratio: 0.70, 95% CI: 0.66-0.75). This corresponds to an additional 6.9 percentage

points (95% CI: 6.0-7.9 percentage points) reduction by colonoscopy screening, compared to sigmoidoscopy screening, or 12 (95% CI: 10-14) fewer CRC cases per 100 000 person-years.

Compared to usual care, the number of CRC cases prevented by colonoscopy screening in women was 31 (95% CI: 21-42) CRC cases prevented per 100 000 person-years, a 23% reduction (rate ratio: 0.77, 95% CI: 0.70-0.85). In men, colonoscopy screening prevented 70 (95% CI: 59-82) CRC cases per 100 000 person-years, a 34% reduction (rate ratio: 0.66, 95% CI: 0.62-0.72), compared to usual care. The sex difference was statistically significant (p-value = 0.02). However, the additional benefit of colonoscopy screening compared to sigmoidoscopy screening, was not different in women (11 [95% CI: 8-14] CRC cases prevented per 100 000 person-years) and men (13 [95% CI: 10-15] CRC cases prevented per 100 000 person-years).

Compared to usual care (no screening invitation), the numbers needed to be invited to colonoscopy screening, to prevent one CRC was 139 (95% CI: 118-164) in women and men combined. In a population that already receive invitation to sigmoidoscopy screening, the number needed to switch to colonoscopy screening to prevent one CRC was 560 individuals (95% CI: 486-661) overall, slightly higher in women (610 individuals [95% CI: 474-853]) than in men (541 individuals [95% CI: 458-661]).

6.2.3 Colonoscopy screening benefits on CRC mortality

Colonoscopy screening, compared to no screening, would avert 15 (95% CI: 11-19) CRC deaths per 100 000 person-years - a 32% reduction in CRC mortality (MRR: 0.68, 95% CI: 0.61-0.76). This corresponds to an additional 7.6 percentage points (95% CI: 5.7-9.6 percentage points) reduction by colonoscopy screening, compared to sigmoidoscopy screening, or 4 (95% CI: 3-5) fewer CRC deaths per 100 000 person-years.

In women the number of CRC deaths prevented by colonoscopy screening was 8 (95% CI: 2-13) CRC cases prevented per 100 000 person-years in, compared to usual care. This corresponds to a 20% reduction (rate ratio: 0.80, 95% CI: 0.67-0.96)). In men, colonoscopy screening reduced mortality by 38% (rate ratio: 0.62, 95% CI: 0.54-0.71), corresponding to 23 (95% CI: 17-29) fewer CRC deaths per 100 000 person-years. The reduction in CRC mortality was significantly greater in men than in women (p-value = 0.04).

Compared to usual care (no screening invitation), the number needed to be invited to colonoscopy screening to prevent one CRC death was 415 (95% CI: 327-567) in women and men combined. In a population that already receive invitation to sigmoidoscopy screening, the number needed to switch to colonoscopy screening to prevent one CRC death were 1611 individuals (95% CI: 1275-2188) overall, higher in women (2248 individuals [95% CI: 1376-6140]) than in men (1300 individuals [95% CI: 1017-1798]).

6.2.4 Validation, colorectal cancer incidence

Individuals not invited to screening in NORCCAP had similar 10-year risk of developing CRC as in the Norwegian portion of NordICC (1.5%). The estimated 10-year effect of colonoscopy screening was 26 (95% CI: 3-49) fewer CRC cases per 10 000 individuals in the simulation model estimate. Observed number of prevented CRC cases in NordICC was 37 (95% CI: 7-68) fewer CRC cases per 10 000 individuals. Corresponding risk ratios were 0.83 (95% CI: 0.70-0.99) in NORCCAP and 0.76 (95% CI: 0.58-0.94) in NordICC.(64)

6.3 Paper 3

Rates of Repeated Colonoscopies to Clean the Colon from Low and High Risk Adenomas - Results from the EPoS trials. Gut 2022;0:1–7. Doi:10.1136/gutjnl-2022-327696

6.3.1 Baseline characteristics

In total, 15 581 patients from 38 endoscopy centers in five European countries were included in the analysis; 6 794 patients with low-risk adenomas and 8 787 patients with high-risk adenomas. Ninehundred-sixty-one patients (961 [6.2%], 95% CI: 5.8%-6.6%) required two or more colonoscopies to achieve clean colon. Individuals with high-risk adenomas were more often scheduled for repeated colonoscopy (n = 825 [9.8%], 95% CI: 9.2%-10.4%), compared to individuals with low risk adenomas (n = 101 [1.5%], 95% CI: 1.2%-1.8%).

6.3.2 Colonoscopy indication and reasons for repeated procedures

Indication for the initial colonoscopy varied by trial (EPoS I versus EPoS II) and country (Table 4). Most common reasons for a repeated (second) colonoscopy were poor bowel preparation

(21.3%), incomplete colonoscopy (including incomplete polypectomy) (14.4%), and polyps left in situ (to be removed in a later colonoscopy) (27.8%). At initial colonoscopy, patients who ultimately underwent two or more baseline colonoscopies had more and larger polyps, compared to patients with only one baseline colonoscopy. Main reasons for a third colonoscopy were piecemeal resection (26.5%) and unspecified reason (23.9%).

Table 4: Indication first baseline colonoscopy per country, across EPoS I and II trials. Numbers are percentages of country total. *(Adapted from Table S1 in Paper 3)*

Indication first colonoscopy	Denmark (n = 1880)	Norway (n = 2888)	Poland (n = 3910)	Spain (n = 6653)	Sweden (n = 250)
Clinical sign or symptom	18.0%	61.3%	2.0%	18.9%	52.4%
Screening colonoscopy	0	2.0%	98.0%	6.3%	42.8%
Other positive screening test	81.4%	28.3%	< 0.1%	74.3%	4.8%
Other	0.5%	8.5%	0	0.4%	0

6.3.3 Clinical practice variation

Need of repeat colonoscopy varied between countries and study centers (Figure 6). In low-risk individuals, the country variation was from 0.5% (95% CI: 0.3%-0.8%) in Poland to 5.2% (95% CI: 3.8%-6.9%) in Denmark. Endoscopy center variation across countries were from 0% to 11.8% (95% CI: 1.5%-36.4%).

In high-risk individuals, country variation was from 2.3% (95% CI: 1.3%-3.9%) in Poland to 15.9% (95% CI: 14.0%-17.8%) in Norway. Endoscopy center variation across countries were from 0% to 63.9% (95% CI: 46.2%-79.2%).

13 904 first baseline colonoscopies in the EPoS I and II trials were performed by one of the 933 endoscopists registered with their name in the trial database. The remaining colonoscopies (879 [12.9%] in EPoS I and 798 [9.1%] in EPoS II) were performed by endoscopists without a trial identification (i.e. endoscopist name). Fewer endoscopists registered in the EPoS I trial, compared to the EPoS II trial, performed 30 or more first baseline colonoscopies: 43 versus 74 endoscopists, respectively. The proportion of repeat colonoscopies following a baseline colonoscopy by each endoscopist varied from 0% to 5.9% in low-risk adenoma patients, and from 0% to 30% in high-risk adenoma patients (Figure 7).

Figure 6: Proportion of patients in EPoS I (low-risk adenomas, panel A) and EPoS II (high-risk adenomas, panel B) trials with two or more baseline colonoscopies at different endoscopy centers in participating countries. Number of centers per country: Denmark 4, Norway 13, Poland 3, Spain 15, Sweden 3. *(Facsimile of Figure 2 in Paper 3)*

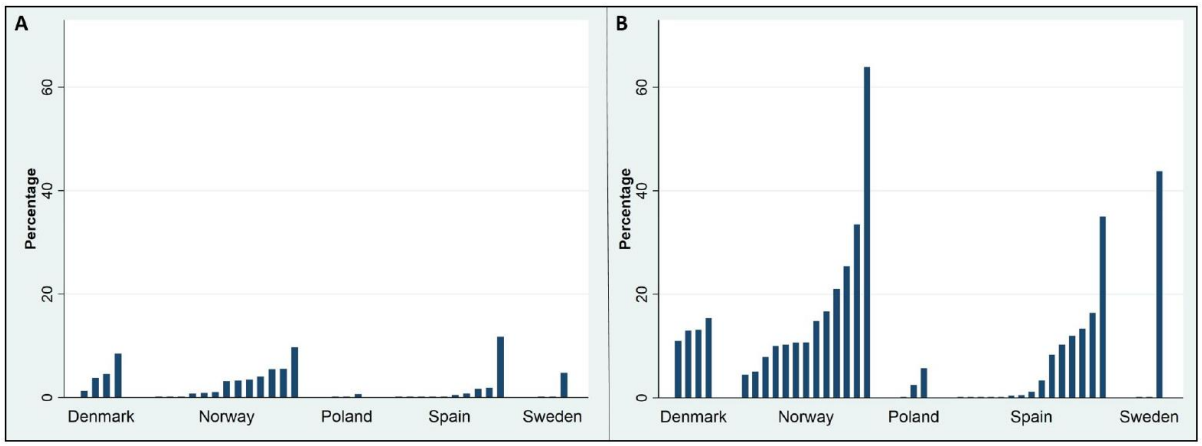
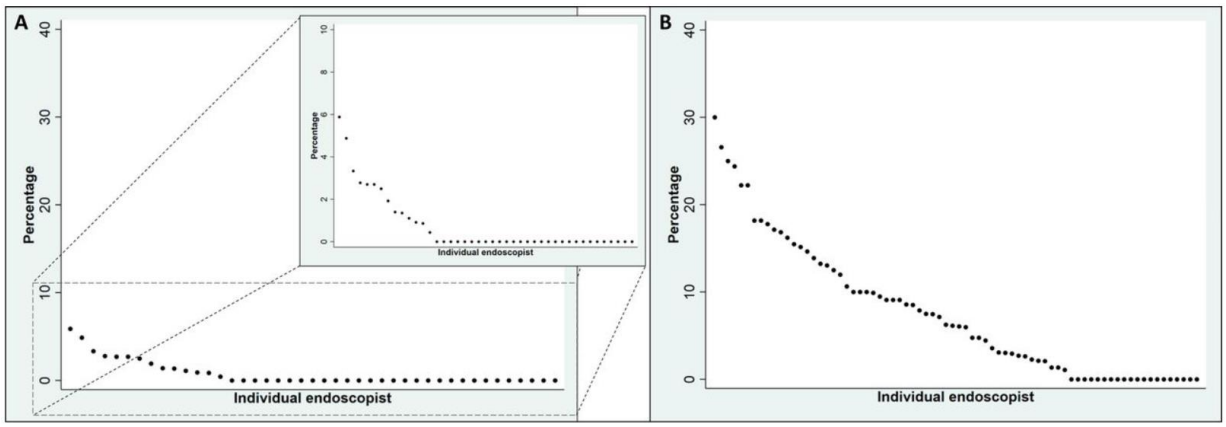


Figure 7: Proportion of patients in EPoS I (low-risk adenomas, A) and EPoS II (high-risk adenomas, B) trials with two or more baseline colonoscopies for participating endoscopists. Number of endoscopists: EPoS I: 43, EPoS II: 74. Inlet in panel A displays differences on smaller scale on y-axis. *EPoS = European Polyp Surveillance*. *(Facsimile of Figure 3 in Paper 3)*



7 Discussion

CRC screening is introduced across the world, and the results of this thesis are highly relevant for policy makers and individuals that undergo such screening. Included papers are linked in that the initial CRC screening procedure (Paper 1 and 2) may trigger downstream steps (Paper 3) related to follow-up or treatment of identified disease. All CRC screening tests (other than colonoscopy) that are positive needs follow-up with a colonoscopy, which put demand on the same endoscopy services.

Four sigmoidoscopy screening trials have previously shown a long-term reduction in CRC incidence and mortality.(53-56) Our pooled analysis in Paper 1 showed that these benefits persists for at least 15 years and our second paper showed that colonoscopy screening can reduce CRC incidence and mortality even more than sigmoidoscopy (approximately 7 percentage points), but three quarters of the colonoscopy screening effect is already achieved by sigmoidoscopy screening. Lastly, our third paper revealed a substantial variation in number of colonoscopies needed to achieve a polyp-free colon before patients can enter post-polypectomy surveillance. Some of the variation was identified as unwanted and possible subject to local audits and endoscopy service quality improvement.

In addition, Paper 1 was the first study to demonstrate a statistical significant reduction in all-cause mortality from CRC screening, which means that screening invited live longer and not only die from other causes than CRC at the same time.(29, 116) Although a 2% relative reduction (mortality rate ratio: 0.98 [95% CI, 0.95 to 1.00], p-value = 0.016) seem small compared to the 20% relative reduction in CRC mortality, deaths from any cause are more common than CRC-specific deaths (14.6% and 0.65%, respectively [usual care group]). As a result, the modest relative reduction translates into a greater absolute reduction in all-cause mortality (rate difference: 0.3 percentage points), compared to CRC-specific mortality (rate difference: 0.13 percentage points). Unlike disease-specific mortality, all-cause mortality is not influenced by the definition of disease, which has been one of the arguments for assessing all-cause instead of CRC-specific mortality.(128) CRC screening programs should be evaluated through mortality (all-cause and/or CRC-specific) rather than survival because the latter is prone to lead-time bias.(29) As described in 5.4.4, lead-time bias is the extra survival time added to individuals with early-detected CRC, before symptoms develop.

The main strength of Paper 1 and 2 is the use of observed outcomes from all published randomized sigmoidoscopy screening trials with long follow-up. Even though trials were performed in four different countries, included individuals came from largely the same birth cohorts which means that improvement in CRC diagnosis and treatment or other time biases that can influence CRC incidence or mortality are less likely. Data from each screening trial had identical definitions of proximal and distal CRC which reduces heterogeneity in Paper 1 and 2.

7.1 Benefits and burdens of endoscopic colorectal cancer screening

Our first two papers exclusively looked at the benefits of CRC screening by endoscopy, while the third paper assessed potential burdens of endoscopy, specifically colonoscopy, as part of a CRC screening program or due to other indications. Even though harms from the screening procedure are rare, some will experience these events when screening is applied to a large population. Further, although it may seem straightforward to follow the principles of screening by weighting harms and burdens against the benefits, individuals differ in their values and put different weight on the burdens and harms.(14, 15, 129)

One could argue that sigmoidoscopy, having less complications than colonoscopy, advocates for the use of colonoscopy as a follow-up procedure only. Sigmoidoscopy and other screening methods like FIT have the benefit of triaging individuals at high risk of CRC, which can be followed by a colonoscopy. Thus, the more resource demanding procedure with higher risk of complications is reserved for individuals with higher CRC risk than the general, average-risk population. However, the complication rate for colonoscopy probably have improved in recent years. For example, there were only one perforation in the NordICC colonoscopy screening trial, where 12 574 participants underwent screening colonoscopies.(64)

In contrast, repeated colonoscopies like we observed in Paper 3 increase the risk of complications. Furthermore, the individual's perceived risk of cancer and benefits of screening may be exaggerated.(130) Unfortunately, cancer screening guidelines – and especially CRC screening guidelines - often put less emphasis on the harms of screening or do not consider them at all when making their recommendations.(110)

Screening for CRC and other diseases involves the risk of overdiagnosis.(18, 29) Overdiagnosis in screening occur when the screening procedure detects disease that would not cause symptoms or contribute to the individual's death if screening was not performed. In these individuals, screening does not give any benefit but may still cause the previously described harms. Unfortunately, overdiagnosis is impossible to detect at an individual level and often difficult to detect at a system level.(131) In a population with an implemented screening program (i.e. without a control group of screening naïve individuals), overdiagnosis may result in an overestimation of the screening benefits.(132, 133) Evaluation of overdiagnosis in endoscopic CRC screening programs is especially complicated because the test work through both prevention and early detection that affect incidence in different directions: prevention decrease CRC incidence, while early detection (potentially) increase CRC incidence (see 3.2.2 and 8.5.1).(133) It is very difficult to disentangle the relative contribution of the two to the observed incidence in the screened population. Although the prevalence of colon polyps is higher compared to CRC, removal of polyps (i.e. "treatment") is less invasive than the removal of CRC. Thus, one could argue that the overdiagnosis of polyps is less severe than the overdiagnosis of CRC.(116)

7.2 Sex differences in screening effectiveness

As stated in the introduction, women have a lower lifetime risk of developing CRC than men, and the 15-years cumulative incidence rates were 1.84 cases per 100 women and 2.9 cases per 100 men in the usual care group (Paper 1 and 2). As a result, the number of CRC that can be prevented in an average-risk screening population such as in our Paper 1 and 2 is higher in men than in women, which makes it even more important to assess screening effectiveness not only in relative comparisons (e.g. rate ratios), but also in absolute numbers (e.g. rate differences). Indeed, the confidence intervals of the sex-specific relative reduction in CRC incidence by sigmoidoscopy screening were overlapping (IRR_{women}: 0.84 [95% CI: 0.77-0.91], IRR_{men}: 0.75 [95% CI: 0.70-0.81]), while the confidence intervals were separate for the absolute reduction, in which the reduction in men was nearly three times the reduction in women (rate differences: 0.75 [95% CI: 0.56-0.93] per 100 men and 0.29 [95% CI: 0.15-0.44] per 100 women).

Previous studies have shown that men, compared to women, have higher number of adenomas overall (15% of men, versus 6% of women) and a larger proportion of adenomas are located in

the distal colon (73% of adenomas in men, versus 40% in women).(134, 135) Another study indicated that nearly half (47%) of CRC cases in women were in the proximal colon (i.e. cecum, ascending colon or transverse colon), which is not within reach of a sigmoidoscopy.(2) Furthermore, in women, advanced neoplasia in the distal colon is not predictive of an advanced neoplasia in the proximal colon.(135) Without any lesions in the distal colon, sigmoidoscopy screening will not result in a follow-up colonoscopy that can detect proximal lesions. Indeed, in the sigmoidoscopy screening trials, we observed a higher number of distal CRC in men (2.1%), compared to women (1.1%), and more men than women were referred for colonoscopy after sigmoidoscopy screening.

Interestingly, the number of proximal CRC in individuals with a negative screening test (Figure 2, group [D]) were slightly higher in women (0.9%) than men (0.8%), and as a result, our colonoscopy screening simulation indicated a larger additional reduction in CRC incidence in women (8.4 percentage points), compared to men (5.8 percentage points). This finding may be an argument for colonoscopy as the primary screening test in women. However, colonoscopy in women is known to be more challenging, compared to men, which may be due to anatomical differences.(136) This may reduce the effectiveness of colonoscopy in women, either as the primary screening method or as follow-up to sigmoidoscopy.(136, 137) In addition, a larger proportion of CRC in women may develop through the serrated pathway, which is harder to detect at endoscopy than traditional adenomas.(58, 138)

A lower attendance rate is believed to attenuate the effectiveness of screening.(139) Attendance rates in women are slightly lower than in men (difference from 4 to 7 percentage points) in all sigmoidoscopy screening trials except NORCCAP, in which attendance rates were 4 percentage points higher in women than in men. However, the sex difference in sigmoidoscopy screening effectiveness were stronger in NORCCAP, compared to the other three trial (Supplement Table 3 in Paper 1), and the per-protocol analysis in the original trial publication also showed lower effect in women.(55)

Our results are in line with previous analysis on screening trials using sigmoidoscopy or FOBT that have indicated a lower effectiveness in women, compared to men.(37, 55, 140, 141) Specifically, our trial is not the first to show no effect on CRC mortality in women invited to

screening.(55, 140, 141) Results from randomized clinical trials on the effectiveness of colonoscopy screening by sex are still pending,(64) but observational studies indicate a sex difference in effect.(135, 142-144) The evidence taken together, it seems timely to start discussing whether CRC screening strategies should be sex specific.(145)

7.3 Colorectal cancer screening age

Our main analyses in screening effectiveness included individuals age 55-64, which is within the broader range of different countries' recommended CRC screening age.(146) Our results did not change when we included individuals 50-54 years old in NORCCAP or 65-74 years old in PLCO, or when comparing the age groups 55-59 years (rate difference 0.50 per 100 individuals) to 60-64 years (rate difference 0.53 per 100 individuals), meaning that the relative effectiveness of screening seems to be quite consistent for different strata. Therefore, there is probably value of extrapolating our (relative) results also to age-groups other than 55-64 year olds.

CRC incidence has been reported to increase in individuals younger than 50 years, especially in males.(147, 148) In Norway, for example, CRC incidence in ages 20 to 49 years increased by 1.9% annually from years 2008 to 2017.(147) However, although the CRC incidence in younger individuals is increasing, the absolute increase and number of CRC cases is small, compared to the number of CRC cases occurring in older individuals.(147, 148) Returning to Norway as an example, number of CRC cases in 2020 were 255 (7.4 per 100 000 individuals) in age group 20-49 years, compared to 4720 (239 per 100 000 individuals) in age group 50 years or older.(3) In other words, lowering the recommended screening age below 50 years (e.g. to 45 years) would mean to introduce screening to a population with lower risk than in today's recommendations.(149)

Because the 10-year risk of developing CRC is comparable when women are 4-6 years older than men, one could argue that women should be invited to screening at on older age than men.(110) However, in our pooled analysis (Paper 1), the effectiveness of screening in reducing CRC incidence was lower in women aged 60-64 years (rate ratio: 0.76, rate difference: 0.39 per 100 individuals) compared to 55-59 years (rate ratio: 0.91, rate difference: 0.20). In men, we observed no difference between age groups. A previous study found similar results when extending the age groups and comparing age group 50-59 years to 60-74 years.(58) One

explanation for the lower effectiveness in older women may be a higher proportion of proximal CRC in older women, compared to younger women, and compared to men at the same age.(58)

7.4 Post-polypectomy surveillance

There is a difference in the patient population in Paper 3, compared to Paper 1 and 2, in that participants have not only been through an endoscopy procedure as part of a screening program, but also due to other indications (e.g. clinical symptoms). Common to all individuals in Paper 3, and some individuals in Paper 1 and 2, are that they had polyps removed at colonoscopy, and that they will be scheduled for a post-polypectomy surveillance colonoscopy. As for colonoscopies following a positive screening test (e.g. FIT), post-polypectomy surveillance put demand on the same (limited) endoscopy resources as the initial colonoscopy. In fact, dependent on the age group, surveillance of polyps and CRC are now the indication for 20% to 33% of colonoscopies performed in the US.(150) In relation to CRC screening, this emphasize the need to take into account who (and at what interval) that should be put under post-polypectomy surveillance when planning a screening strategy (see also 8.2.1).

However, there is limited evidence that post-polypectomy surveillance actually reduce CRC incidence or mortality,(81, 151), but there is evidence that risk of CRC after colonoscopy is dependent on the quality of the baseline colonoscopy(152) and characteristics of polyp(s) removed at baseline.(153) Paradoxically, repeated colonoscopies to remove all polyps or quality improvement to increase ADR (shown to lower post-colonoscopy CRC risk) will result in more detected adenomas, and subsequently more individuals scheduled for surveillance colonoscopies. Thus, it may be prudent to suggest less aggressive surveillance recommendations as endoscopy quality is improved.(151) Interestingly, a study on individuals with low-risk adenomas revealed that they had lower CRC risk compared to the general population,(88) suggesting that they might not need post-polypectomy surveillance at all.

7.5 Quality indicators in endoscopy

To be included in one of the EPoS trials (Paper 3), participants had to undergo a high quality colonoscopy, meaning a colonoscopy with adequate bowel preparation, cecum intubation and all polyps completely removed. All endoscopy centers in the EPoS trials were (and are) required to have system for monitoring established quality indicators in endoscopy, such as ADR and cecum intubation rate.(39, 89) Our Paper 3 looked at a potential new indicator; number of colonoscopies needed to remove all colon polyps, and revealed a substantial variation between countries, endoscopy centers and endoscopists.

Some repeated colonoscopies are probably warranted, for example due to many or large polyps that are difficult to remove in one session. Not surprisingly, the need of repeated colonoscopies was higher in high-risk individuals, compared to low-risk individuals. Further, the indication for colonoscopy can affect routines and clinical practice, and some endoscopy centers receive larger proportions of some indications than others (e.g. colonoscopy for CRC screening versus colonoscopy due to symptoms), or are more specialized and handle more complicated patients. However, in the EPoS trials, with strict inclusion and exclusion criteria, all included patients share patient and polyp characteristics and are thus fairly similar across centers. We believe it is reasonable to assume that similar polyp characteristics should imply similar number of colonoscopies to remove them all, and consequently that some of the observed variation is unwanted.

Unwanted variation may, for example, be due to differences in endoscopist performance and approach to polypectomy. It is possible that high-performance and confident endoscopists are more comfortable removing large polyps than more uncertain endoscopists, who instead schedule the patient for a repeated colonoscopy. Endoscopists` confidence may also affect the likelihood of scheduling a repeat colonoscopy "just to be sure" that all polyps were completely removed the first time. Unfortunately, individual level data on endoscopists' performance (e.g. endoscopist ADR (39, 154)) were not available for our analysis on number of repeated colonoscopies.

Another possible contribution to the variation is that some endoscopy centers have a common practice of limiting the number of polyps removed in a single session, either due to time restrictions or reimbursement issues.

Monitoring the rate of early repeat colonoscopy may enable endoscopy centers and health care systems to identify areas for improvement. The underlying reasons for frequent repeat colonoscopy can be complex and multifactorial, however, and root cause analyses is necessary to designate quality improvement measures.

7.6 Unwanted variant and root cause analysis

Root cause analyses are several methods to identify causal relationships, for example between short withdrawal time and time allocated to perform the endoscopy,(155) and can be used to identify the cause of a high proportion of repeated colonoscopies before surveillance. The concepts of root cause analysis have been more widely used in industry but in many ways resemble how an epidemiologist identify causal relations between exposure and diseases, or how medical doctors diagnose an individual patient. The goal may be to prevent mistakes from recurring (e.g. error in anesthesia administration (156)) or improve health care quality overall.

Root cause analysis, however, is not without limitations. First, root cause analysis are reactive and retrospective, and may be affected by recall bias, in contrast to a proactive risk assessment to detect and prevent hazards before they occur.(157) The causes are often many and complex, and one should not be misled to think that there is *one* single cause to the problem. Unfortunately, there are large differences in the tools and time used to investigate unwanted events or variation.(157, 158) Identified causes should be assessed together in a system perspective and, through feedback loops, lead to change in practice to prevent the event from recurring.

8 Methodological considerations

8.1 Relevance of sigmoidoscopy screening

Some may argue that sigmoidoscopy screening, the intervention in Paper 1, is no longer relevant. The US population is usually screened by colonoscopy,(146) and the bowel cancer screening program in the UK recently switched to FIT.(33, 159) In Norway, a CRC screening program using FIT is currently being introduced, and the goal of the country's health authorities is to switch to primary colonoscopy screening within the next five years.(160) In fact, to our knowledge no organized screening program use sigmoidoscopy as the primary screening test.(33, 146)

It is, however, not possible to observe the long-term results of the most up-to-date interventions – you have to choose. Long-term results (beyond 10-years of follow-up) of colonoscopy screening for colorectal cancer are not yet available,(64) but it is believed that colonoscopy screening is at least as effective as sigmoidoscopy screening. Thus, our results contribute to the knowledge about the duration of endoscopy screening effects. Furthermore, much can be learned about the effect of current endoscopic screening practices based on the sigmoidoscopy trials, for example through the comparison of sigmoidoscopy to colonoscopy screening in our Paper 2.

8.2 Sigmoidoscopy screening trial differences

Some differences between the four sigmoidoscopy screening trials included in Paper 1 and 2 have already been discussed (e.g. pre- and post-randomization consent), but there are some other traits that need mentioning. Firstly, individuals in the screening group in PLCO were re-invited to a second sigmoidoscopy screening test 3 or 5 years after the first invitation. This second screening round probably explains the increase in CRC incidence 4-5 years after the initial screening round observed in Paper 1.

In addition, 50% of individuals randomized to sigmoidoscopy screening in the NORCCAP trials were randomized to FOBT (not FIT) in addition to the sigmoidoscopy procedure. The combined sigmoidoscopy and FOBT screening group had a slightly higher adenoma yield per participant than sigmoidoscopy only, but slightly lower attendance rate.(107) For the long-term

effect of screening, there was no difference between the groups – neither for CRC incidence, nor CRC mortality.(55)

8.2.1 Positivity threshold

A lower threshold for a positive test (positivity threshold) at screening will results in more referrals to follow-up (e.g. surgery or colonoscopy), which may detect and prevent more cancer cases, but also increase cost.(161) The thresholds for a positive screening test differed in the four sigmoidoscopy screening trials included in Paper 1 and 2, and the only criterion for a positive screening test that was present across trials was CRC identified at sigmoidoscopy.(53-56) In all trials except PLCO, a positive test meant referral to follow-up colonoscopy, whereas in PLCO individuals were referred back to their general practitioner (who usually referred the patient to colonoscopy). In PLCO, any polyp or mass was counted as a positive screening test, while the other trials only referred individuals with polyps ≥5- or ≥10mm in size, or polyps identified as adenomas.

As a result, the proportion of participants who underwent colonoscopy was higher in NORCCAP and PLCO than in UKFSST and SCORE.(53-56) It is interesting to note that the latter trials (i.e., in UK and Italy) with more stringent positivity thresholds (which resulted in much lower rates of colonoscopy requirement) delivered comparable magnitudes of benefit compared to programs with less stringent positivity thresholds. This might suggest that sigmoidoscopy screening programs should adopt more stringent positivity thresholds to reduce the number of colonoscopies while preserving the benefits of reducing CRC incidence/mortality.

Similarly to the positivity threshold at screening, the threshold for post-polypectomy surveillance will influence the number of colonoscopies: A lower threshold to enter surveillance will result in more (surveillance) colonoscopies, which also increase the risk of overdiagnosis.(133) Furthermore, shorter and/or more frequent surveillance intervals will add to the number of colonoscopies. The main objective of the EPoS trials is to investigate the effect of different post-polypectomy surveillance strategies in CRC incidence.(89)

To identify and include all test traits and downstream consequences (e.g. post-polypectomy surveillance) of different screening approaches to identify the most cost-effective is no

simple task, and individual and societal values and preferences should be taken into account.(66, 72, 129, 162, 163)

8.3 Contamination in randomized trials

In randomized trials, there is a possibility of contamination in the control group. Contamination is defined as the receipt of active intervention in individuals randomized to the control group.(164) Contamination in a colorectal cancer screening trial would mean that individuals randomized to no screening (control group) undergo a screening procedure (e.g. FIT or colonoscopy) similar to individuals randomized to screening. Similarly, in the EPoS trials investigating different surveillance intervals, individuals randomized to the longer interval, but who (outside the trial) undergo a surveillance procedure at an earlier time point will contribute to contamination of the trial result.

None of our studies were able to assess screening contamination in detail. Screening contamination in the usual care group in Paper 1 and 2 was probably higher in PLCO and SCORE than in the other two trials because of opportunistic screening in the general population. A national screening program was introduced in the UK and Norway during trial follow-up but special precautions were taken to limit the contamination by not inviting trial participants to a new screening test (as part of the national program). Still, the effect of sigmoidoscopy screening on CRC incidence and mortality reduction is remarkably similar in all trials.(53-56)

8.4 Attendance rate and screening effectiveness

Even after signing informed consent, attendance in large clinical trials like the screening or surveillance trials included in this thesis will never be 100% - some will refuse or ignore the invitation to participate, or are lost to follow-up. Reasons for not attending may be that the individual does not want to go through an unpleasant endoscopy procedure or prioritization of conflicting activities at the day of the scheduled screening procedure.

Earlier studies have not shown a linear correlation between attendance rate and effectiveness of CRC screening, which may be explained, at least in part, by the risk of the individuals that attend. Several studies have shown that those who attend screening have different characteristics and risk factors, compared to individuals not attending.(27, 165) However, the polish individuals

attending colonoscopy screening in the NordICC trial seemed to have higher CRC risk, compared to individuals not attending.(64)

For our simulation study (Paper 2), we assumed that screening attendance with colonoscopy would be equal to the screening attendance observed in the sigmoidoscopy trials. However, this is probably too optimistic. The trend is that the attendance rate is falling the more invasive the screening procedure is (e.g. FIT compared to colonoscopy screening (166)), and if the procedure needs to be repeated.(70) The NordiCC trial, for example, had an overall attendance rate of 40%, ranging from 23% in the Netherlands to 61% in Norway.(48) Further, existing CRC screening programs (which primarily use FIT),(33, 146) and ongoing studies on colonoscopy screening have similar or lower attendance rates.(63, 166)

8.5 Endoscopy effectiveness in distal and proximal colon

Our colonoscopy screening simulation model assumes that a screening colonoscopy and colonoscopy performed after a positive sigmoidoscopy screening will have similar sensitivity for adenomas and cancer. It is reasonable to think, however, that a colonoscopy following a positive screening test may be more meticulous because the probability (risk) of pathological findings is higher, compared to primary colonoscopy screening in an unselected, average-risk population.(108) Interestingly, cecum intubation rates have been found to be similar in primary screening colonoscopies and colonoscopies with a clinical indication (e.g. symptoms).(167) Cecum intubation rate is a quality indicator independent of the prevalence of pathological findings, and low cecum intubation rates have been shown to be associated with risk of distal or proximal CRC.(39, 168) Another indicator, ADR in the distal colon, was slightly higher in a colonoscopy screening trial, compared to sigmoidoscopy screening.(48, 124)

It may be further argued that the more complete bowel preparation before a colonoscopy result in a cleaner distal colon that is easier to examine adequately compared to bowel preparation before sigmoidoscopy. However, there were not many individuals with a negative sigmoidoscopy screening test who were later diagnosed with cancer in the distal colon. In other words, there are not many remaining distal CRC cases to prevent in a population where sigmoidoscopy screening has already been introduced. Furthermore, as seen in Paper 3, poor bowel preparation is also a challenge in colonoscopy.

Our last assumption in the simulation model was that colonoscopy screening effect in the proximal colon was similar to the effect of sigmoidoscopy screening in the distal colon. This assumption may be an overestimation, for example due to more difficult working conditions in the proximal colon, compared to distal colon, different carcinogenetic sequences, or because the proportion of proximal cancers increase with age.(169)

8.5.1 Early detection versus prevention

Some individuals attending screening will have CRC detected at screening that would present with symptoms without the screening program. These prevalent cancers are the main reason for the increased incidence in the screening group at start of follow-up. It has been argued that these prevalent cancer cases should not be included in our CRC incidence analysis because they are not "true" incident cancer - screening cannot prevent what is already present at screening.(170)

As observed in Paper 1, the yearly CRC incidence in the screening group is reduced after the first year of follow-up. This reduction is due to early detected cancers (cancers detected and removed at screening cannot be detected at a later time-point) and due to removal of precursor lesions, which are prevented from developing into CRCs. The relative contribution of the two mechanisms in terms of reduction in CRC mortality is difficult to measure but over time, prevention plays a larger role than early detection.(171) Further, in the four sigmoidoscopy screening trials, we only examined the left colon, which means that right sided cancers may have been prevalent in the early years but not detected in the screening arm initially. To take this into account would make our calculations even more complicated.

In summary, it would be problematic to exclude cancer cases detected at screening from our calculations based on an arbitrary approach to the definition of CRC incidence. Regardless of method, screening is not perfect and some CRC are missed.(172-174)

8.6 Statistical analyses

8.6.1 Pooled data versus meta-analysis

We used different analytical approaches in Paper 1 and Paper 2, namely pooling of data and meta-analysis, respectively. When planning the analysis in Paper 1 we decided to pool the data

rather than to perform a meta-analysis in order to maintain flexibility with regards to analyses and presentations (i.e. yearly and cumulative plots). The need for usual care group size reduction have been described previously (see 5.1.3). One could argue that our pooling approach made it easier to create yearly and cumulative rate ratio plots, but it would also be possible to estimate the yearly rate ratios by a repeated (yearly) meta-analysis approach. Our sensitivity analysis using a meta-analysis approach on the same data gave similar results as our pooled analysis (Supplementary Table 1 in Paper 1).

Contrary to the main analysis in the first paper, we pre-specified that we wanted to use a meta-analytical approach in Paper 2. The choice made us able to include and analyse data from the total follow-up time in all four trials. Meta-analyses are usually performed under one of two assumptions of the true effect size that each trial included in the analysis are measuring: Either, one can assume that there is only *one* true effect size (fixed effect model) underlying the trials' estimates, or that each trial estimate different underlying effect sizes (usually assumed to have a normal distribution) (random effect model).(175, 176) In a fixed effect model, trials are weighted based on the variance (i.e. precision) of their effect estimates only, while a random effect model also include the variance of the underlying effect estimates. Accordingly, less variance (such as in larger studies) are given more weight in a fixed effect model, compared to a meta-analysis using a random effect model. Further, the summary estimates of a random effects model will have a wider – more conservative - confidence interval than using a fixed effect model. The difference between the two models will be larger the greater the heterogeneity between the individual trial estimates are.(175, 176)

Heterogeneity can be assessed through statistical methods (e.g. Cochrane Q or I^2), but should also be assessed through evaluation of the methodological aspects of the trials. For example, the four sigmoidoscopy screening trials included in our analysis had similar intervention (sigmoidoscopy) and outcome measures, and relatively similar effect estimates with overlapping confidence intervals - all arguments for using a fixed effect approach. However, the trial randomization procedures, trial populations (CRC risk, access to health care, etc.) and positivity thresholds differed between the trials. Taken together, we chose to use the conservative approach of a random effect model.

8.6.2 Data handling

We used all available data from the latest publications of the four sigmoidoscopy screening trials in Paper 1 and 2. Data from most trials were shared as two datasets:

1. Total cumulative data with complete follow-up (e.g. number of events, individuals at baseline and person-years of follow-up)
2. Aggregated, 1-year data (e.g. number of individuals at risk at the start of the year and number of events occurring during the year)

The advantage of the first dataset was the accurate and complete follow-up data from all trials. However, the dataset did not allow us to make yearly or cumulative incidence or mortality plots.

The granularity of the UK data in the second dataset was hampered by new data sharing regulations, which only allowed data shared as 3-year aggregated intervals (due to many small data cells if a yearly interval was used). To be able to use the 1-year granularity of the other trials, we split the UK data equally into each year, within the 3-year interval. For example, for the follow-up years 4-6, the number of CRC cases and the reduction in number for individuals at risk (i.e. difference from number at risk at the following years 7-9) were equally distributed between the individual years. This is probably an adequate solution because previous publications do not show any abrupt change in the year-to-year number of events.(54)

Our approach to the UK CRC incidence in years 1-3 was an exception because, as seen in all sigmoidoscopy screening trials, the incidence in screened individuals increase the first year, due to screening detected CRC. To take this into account, we first subtracted the previously reported number of screening detected CRC,(54) before splitting the remaining number of events equally between years 1, 2 and 3. All screening detected CRCs that were initially subtracted from the aggregated number (years 1-3) were then added to the number of events in year 1.

Even though data were aggregated into three-year periods, some subgroup UK data cells had seven or fewer individuals, which meant that the exact number could not be shared. As

a result, analysis on CRC mortality by site was performed without data from the UK trial, which comprised 42% of all individuals included in the analysis. Inevitably, due to the reduced number of individuals, the resulting CIs in CRC mortality by tumor location were wider than the other estimates. We did not see any solution that would allow us to accommodate the UK regulations. Three remaining cells with 7 or fewer events were set to the value of seven in the analysis. It is unlikely that the resulting small overestimation of the total numbers of distal CRC cases and overall CRC deaths in the UK data made substantial a difference to the analysis results or conclusion.

Another challenge with the 3-year aggregated data was that the latest follow-up years were not specified more than "≥16 years". We would have to do several assumptions to this follow-up period with high uncertainty (e.g. number of individuals at risk at the beginning of year 17, 18, 19, etc.) if these data were to be included in our pooled analysis on yearly data (Paper 1).

We believe it would be more complicated and potentially confusing for the reader if we used two different datasets with different follow-up time in one paper. As a result, Paper 1 did not include data beyond 15-years of follow-up, to allow the presentation of yearly- and cumulative incidence and mortality plots with data from all trials. In Paper 2 we used the cumulative data, to achieve a more accurate estimate with the longest available follow-up time.

In Paper 3, we chose to exclude individuals with adenomas ≥ 20 mm at Polish centers from the analysis because local policy required that these patients were referred for a second colonoscopy. As a result, the remaining Polish data included in our analysis may be different from the data from the other countries, as patients with such lesions in the other countries are more likely to require a second colonoscopy. However, the contribution of patients with such polyps was only 6.2% (excl. Poland) and probably does not make a major impact on our results.

We also decided to exclude individuals at two Norwegian sigmoidoscopy screening centers because these individuals had already been to an endoscopic procedure (sigmoidoscopy) were polyps could have been removed. This would lead to a reduced number of polyps in the distal colorectum in need of removal at follow-up colonoscopy, which would make it difficult to interpret the number of repeated colonoscopies needed to remove all polyps.

8.6.3 Bootstrapping

In Paper 2, we used bootstrapping to calculate the variance of the colonoscopy screening effect (e.g. rate ratio), compared to sigmoidoscopy screening or no screening invitation. Statistical bootstrapping is a way to estimate variance, the basis for standard errors and CIs through a resampling procedure on the available data.(177) In theory, we could have used a standard meta-analysis approach to estimate the overall rate, rate difference and NNS. The problem is that it is not straightforward to compute the weights because the variance of the colonoscopy estimates is complicated, that is; because the colonoscopy estimates involve multiplying a count by the distal sigmoidoscopy rate ratio, which is not independent of the overall rate ratios. However, by using bootstrapping to estimate the variances of all the colonoscopy metrics, we could proceed as for the sigmoidoscopy screening estimates.(177) We assumed Poisson distributions for the number of distal, proximal and unknown location events in each group (Figure 2, groups [A] to [D]), which should be essentially independent of each other.

8.6.4 Intention-to- treat vs per-protocol

Our results in Paper 1 and 2 are based on the intention-to-treat principle, which means that all individuals randomized to the intervention group (invitation to screening) are compared to all individuals randomized to the control group (no screening invitation). An alternative approach is the per-protocol comparison, in which only individuals who comply with the intervention are included in the analysis. In our studies this would mean that individuals not attending screening (Figure 2, group [B]) are excluded from analyses. In Paper 1, yearly data on whether the individuals at risk had attended screening or not were not available because sharing these data would imply small data cells incompatible with data sharing regulations. Accordingly, we could not calculate or exclude these individuals (or their events) to perform a per-protocol analysis.

Even if data were available, we would choose the intention-to-treat approach in both papers because we wanted to examine the real-world effectiveness of offering sigmoidoscopy or colonoscopy screening, not the effect of screening itself. The latter is the interpretation of the results from a per-protocol analysis. The results of an intention-to-

treat analysis depend on all the factors that influence if an individual attends or not (both those we know about and possibly can measure such as gender and age, and those we do not know about or cannot measure such as different lifestyle choices, genetics), in addition to the effect of the screening intervention itself.(178) As previously described, much research have demonstrated that screening attenders differ from non-attenders, not only in CRC screening programs, an important difference being the CRC risk.(27, 165)

The CRC risk among attenders will influence the result of a per-protocol analysis: if healthy, low risk individuals attend, the estimated screening effect will increase, while the estimated effect will decrease if mostly high-risk individuals attend. Since those who attend screening are a subset of those randomized to screening, an unbiased estimate of the efficacy of screening would require identification of those same individuals in the usual care group (i.e. those who would attend screening if given the opportunity).(178) This has proven to be very challenging in screening trials, of which many are conducted in populations where a screening program has already been implemented and thus no control group exists. Our use of an intention-to-treat approach can explain the slightly lower effectiveness of CRC screening seen in our studies (Paper 1 and 2), compared to previous model studies.(179).

8.6.5 Absolute and relative effect estimates

In Paper 1 and 2, we looked at both absolute and relative estimates, for example rate differences and rate ratios, respectively. This is important because, as has been shown for all-cause mortality, age- and sex-specific effects, the numbers depend on baseline risk, which is the risk without any intervention. For example, an intervention on a low risk disease may result in a large relative change in risk, but a small change in absolute risk. Similarly, for a high risk disease even a small change in relative risk will correspond to a large change in absolute risk. This is highly relevant in screening programs because the resources needed to prevent one event (i.e. numbers needed to screen) increases if the prevalence of adenomas and CRC is reduced, for example by screening at a younger age. The same principles and distinctions are applicable to analysis on subgroups with different risks (e.g. sex).

In principle, rate differences are not affected by prevalent cancer detected at screening because, assuming no overdiagnosis, these cases will ultimately present themselves in the follow-up

period and thus contribute with an equal number of cases in the screening and usual care groups.(170) This makes rate difference more relevant when evaluating cancer screening in a public health perspective.

8.6.6 Crude versus adjusted analysis

We did not perform any adjustments in our analyses, meaning that we did not adjust for contamination, patient, polyp, or other baseline characteristics. In principle, this is unnecessary in the two first papers because they were based on intention-to-treat analysis from randomized trials where all baseline characteristics are equally distributed between the screening and no-screening groups.

The trial populations in the sigmoidoscopy screening trials using post-randomization consent probably differ from the general population, which is the population that will be screened in a regional or national screening program. One could try to adjust for known differences between the trial and general population in the analyses, similar to adjusting for non-compliance in case-control studies on screening programs.(25, 26) However, there is no way of testing whether the adjustment you make is correct and sufficient, or not.

Paper 3 had an exploratory approach on investigating clinical practice variation. The purpose of such studies is to reveal variation (if present), not to analyze or definitely understand the causal pathways of an identified variation. Our interests were in outliers (centers or endoscopists), not in the variation itself or the mean or median values. In fact, even a variation analyses showing no outliers is no guarantee for good performance because all centers/endoscopists could do it poorly.

9 Conclusion and implication of results

Colorectal cancer screening and surveillance are dependent on each other as parts of an individuals' treatment path. The decision to start colorectal cancer screening or not, and to choose the optimal screening method for the local setting, are no easy choices. Although colonoscopy screening may provide the greatest benefits in terms of reduced CRC incidence and mortality, it is too early to conclude that colonoscopy is the best screening approach at a population level.

Our studies show that sigmoidoscopy screening have a long lasting effect on CRC incidence and mortality, and may be a valid option to colonoscopy screening. Using sigmoidoscopy as the initial screening test reserves endoscopy resources for individuals at higher risk of CRC, or individuals in need of more than one colonoscopy to have all polyps identified and removed at a high quality colonoscopy.

Furthermore, the work included in the current thesis revealed variations in number of colonoscopies needed remove all polyps which may be available for quality audits and improvement, to reduce number of repeated colonoscopy procedures.

10 Future perspectives

Colorectal and other cancer screening programs are resource demanding. Benefits, harms, burdens, available resources, work-up surveillance and individual preferences should be evaluated together when planning a screening program. The long-term results of the NordICC trial and primary analyses of other colonoscopy screening trials will add to the knowledge about benefits and harms of colonoscopy screening.

In the future, it will be interesting to look at number of colonoscopies at baseline and long-term CRC incidence and mortality - the primary endpoints in the EPoS I and II trials. If the number of baseline colonoscopies are strongly linked to CRC mortality or other important outcomes, it may be timely to discuss if it should be included as a quality indicator, and what proportion that is representative of good quality.

With limited colonoscopy resources the question remains as to who should be prioritized for the procedure, and how to get high-risk individuals to attend screening. For example if high-risk individual's surveillance should be prioritized in front of a person with a positive FIT, but who is without previous risk factors. Some have suggested to apply machine learning to flag persons at highest risk and thus in highest need of colonoscopy.(180) It will be highly relevant to investigate the number of colonoscopies needed to achieve clean colon at surveillance.

A randomized trial directly comparing sigmoidoscopy and colonoscopy screening would be the methodologically most valid comparison of the two screening methods, but it is difficult to conduct without a large risk of screening contamination, now that screening programs are being implemented worldwide. After screening is introduced in an area, there is no longer a control group similar to the sigmoidoscopy screening trials included in our analysis. Implemented screening programs should be "learning", to further improve knowledge and performance of screening.(161, 181)

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12 Paper*s*

Paper 1

15-Year Benefits of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality: A Pooled Analysis of Randomized Trials

Ann Intern Med.2022;175:1525-1533. [Epub 11 October 2022]. doi:10.7326/M22-0835

Paper 2

15-year Effectiveness of Colonoscopy Screening on Colorectal Cancer Incidence and Mortality - Simulation Analysis of Four Sigmoidoscopy Trials

Manuscript in review, December 2022.

Paper 3

Rates of Repeated Colonoscopies to Clean the Colon from Low and High Risk Adenomas - Results from the EPoS trials

Gut 2022;0:1–7. doi:10.1136/gutjnl-2022-327696