The Risk of Colorectal Cancer Incidence and Mortality after Screening and Adenoma Removal

A Doctoral thesis by

Henriette C. Jodal

Institute of Health and Society

Faculty of Medicine

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At the very end of medical school, I was fortunate to get to know my co-supervisor Michael Bretthauer through a student assignment. His enthusiasm and eagerness for critical thinking and research was contagious, and he soon invited me to join a group meeting with the Clinical Effectiveness Research Group. In this group, the ideas are many, the discussions both broad and wide, and the openness remarkable. I was introduced to my main supervisor Magnus Løberg, who just then was finishing his doctoral degree, and through his patient guidance my understanding of epidemiology started to grow. Mette Kalager, as the inspiring head of the research group and an expert in epidemiology, also became my co-supervisor. Through these years, the three of them have made an extraordinary supervisor team, all with their own area of expertise, complementing each other.

Through 2017 and 2018 much of my research life consisted of travelling to different Norwegian hospitals and studying patient charts from sunrise to sunset, and a bit longer. The fond memories of this time are all due to my amazing colleagues; Sofia E. Olsen and Magnhild Herfindal.

In 2019 my family and I travelled to Boston and stayed for 6 months. During this time research and family became one, due to Mette and Michael's including behaviour and invitations to events with their family, and the collaboration and fellowship of my colleagues Paulina Wieszczy and Lise M. Helsingen with family.

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Through these years, I have collaborated, discussed and met many amazing persons, at the office, in Boston, and at hospitals throughout Norway. I will always feel forever thankful to everyone who made this research possible. I thought myself grown-up when I left medical school. However, these years as a PhD candidate has challenged me to grow and become the person I am today.

My parents, Helle and Stein, taught me to be strong-willed and never give up. Through all this, there is one person who has always been my steadfast support, keeping me sane: my husband Stian. I will forever be grateful to you for taking care of me, and our family, in particular staying at home with a 1-year-old while I was reading patient charts, and a 4-month-old during our stay in Boston. Thank you for giving me Johan, Sonja and "lillebror", while I have been busy pursuing my goals.

Oslo, September 2021

Henriette C. Jodal

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1 Abbreviations

ADR	Adenoma detection rate
BMI	Body mass index
BMJ	British Medical Journal
CI	Confidence interval
CT	Computer tomography
ESGE	European Society of Gastrointestinal Endoscopy
FIT	Faecal immunochemical test
FOBT	Faecal occult blood test
gFOBT	Guaiac faecal occult blood test
HR	Hazard ratio
iFOBT	Faecal immunochemical test
NMA	Network meta-analysis
NORCCAP	NORwegian Colorectal CAncer Prevention trial
NSAIDs	Non-steroidal inflammatory drugs
PSA	Prostate-specific antigen
RCT	Randomised controlled trial
REML	Restricted maximum likelihood
RR	Relative risk
SAR	Surveillance after Adenoma Removal study
SIR	Standardised incidence rate
SMR	Standardised incidence-based mortality rate
USMSTF	US Multi-Society Task Force

1 Thesis Summary

Background

Colorectal cancer is a major health burden worldwide. Norway has one of the world's highest rates of colorectal cancer, with a cumulative risk of 5.0% for men and 4.0% for women before 75 years of age. 60-75% of colorectal cancers develop from precursor lesions known as adenomas. Screening for colorectal cancers have been implemented in many countries to decrease the risk of colorectal cancer incidence and mortality. Still, individuals who have been screened may develop an interval cancer, i.e., a cancer presenting in the interval after a screening episode. In addition, surveillance programmes after adenoma removal have been introduced. In this thesis, I aim to investigate the effect of colorectal cancer screening and adenoma removal, and the risk of colorectal cancer death from an interval cancer.

Methods

We performed a systematic review of existing randomised controlled trials (RCTs) on colorectal cancer screening among healthy individuals aged 50-79 years. We performed a network meta-analysis (NMA) of different screening methods using a random-effects model. Follow-up >5 years was required for analysis of colorectal cancer incidence and mortality. A subgroup analysis of men and women was performed. Within an established RCT on sigmoidoscopy screening, the NORwegian Colorectal CAncer Prevention (NORCCAP) trial, we performed a secondary analysis comparing colorectal cancer and all-cause mortality among individuals with interval cancers to individuals with colorectal cancer in the control group of the trial, using Cox proportional hazard regression adjusted for sex and age. Through the Cancer Registry, we identified all individuals in Norway who had adenomas removed between the years 1993-2007, and followed them through 2018. We calculated standardised incidence (SIR) and incidence-based mortality ratios (SMR) for colorectal cancer among women and men, compared to the general female and male population.

Results

The systematic review revealed 12 eligible RCTs on colorectal cancer screening with guaiac faecal occult blood test (gFOBT), faecal immunochemical test (FIT), sigmoidoscopy and colonoscopy. Only RCTs on gFOBT and sigmoidoscopy had sufficiently long follow-up to evaluate colorectal cancer incidence and mortality. We found that sigmoidoscopy screening slightly reduces colorectal cancer incidence and mortality, while gFOBT screening slightly reduces colorectal cancer mortality, but does not affect colorectal cancer incidence. The effect of sigmoidoscopy screening was larger in men than in women. The secondary analysis of the NORCCAP trial included 163 individuals with interval cancer and 1740 individuals with colorectal cancer in the control group. Colorectal cancer mortality and all-cause mortality were similar between the two groups. The cohort of individuals who had adenomas removed comprised 40,293 individuals. Compared to the general female and male population, colorectal cancer incidence was increased among both women and men who had had adenomas removed, but the increase was more pronounced in women than in men. Colorectal cancer mortality after adenoma removal was increased in women and reduced in men, compared to the general female and male population.

Conclusions

We found that colorectal cancer screening with gFOBT and sigmoidoscopy had a long-lasting effect of at least 15 years. Individuals who experienced an interval cancer after a negative screening exam had similar prognosis to clinically detected cancers. Both sigmoidoscopy screening and adenoma removal had less effect in women than in men, thus sex-specific screening and surveillance should be considered.

2 Sammendrag av avhandlingen

Bakgrunn og mål

Tykk- og endetarmskreft er en stor verdensomspennende helsebyrde. Norge har en av verdens høyeste rater av tykk- og endetarmskreft, med en kumulativ risiko på 5.0 % for menn og 4.0 % for kvinner før 75-årsalder. 60-75 % av tarmkreften utvikles fra forstadier kjent som adenomer. Tarmkreftscreening har blitt innført i mange land for å redusere risikoen for tarmkreftinsidens og -mortalitet. Likevel kan personer som har blitt screenet utvikle en intervallkreft, det vil si kreft som oppstår klinisk i intervallet etter en screeningepisode. I tillegg har det blitt innført overvåkningsprogrammer av personer etter adenomfjerning. I denne avhandlingen, undersøker jeg effekten av tarmkreftscreening og adenomfjerning, og risikoen for tarmkreftmortalitet fra en intervallkreft.

Metoder

Vi lagde en systematisk oversikt av randomiserte kontrollerte studier (RCT) på tarmkreftscreening blant friske personer i alderen 50-79 år. Vi gjorde en nettverksmetaanalyse (NMA) av ulike screeningmetoder hvor vi brukte en tilfeldig effektmodell. Vi krevde oppfølgingstid >5 år for å evaluere tarmkreftinsidens og -mortalitet, og gjennomførte en subgruppeanalyse på kvinner og menn separat. Vi gjorde en sekundæranalyse innenfor en etablert RCT på sigmoidoskopiscreening, NORwegian Colorectal CAncer Prevention (NORCCAP)-studien, hvor vi sammenlignet tarmkreftmortalitet mellom personer med intervallkreft med kreft hos personer i kontrollgruppen av studien, ved bruk av Cox proporsjonal hasard regresjon justert for kjønn og alder. Vi identifiserte alle personer i Norge som hadde fått fjernet et adenom i perioden 1993-2007 gjennom Kreftregisteret, og fulgte dem gjennom 2018. Vi beregnet standardiserte insidens- (SIR) og insidensbaserte mortalitetsratioer (SMR) for tarmkreft hos kvinner og menn, sammenlignet med den generelle kvinnelige og mannlige populasjonen.

Resultater

Den systematiske oversikten inkluderte 12 RCTer på tarmkreftscreening med guaiac-farget avføringsprøve (gFOBT), immunkjemisk avføringsprøve (FIT), sigmoidoskopi og koloskopi. Bare RCTer med gFOBT og sigmoidoskopi hadde lang nok oppfølgingstid til å evaluere tarmkreftinsidens og -mortalitet. Vi fant at sigmoidoskopiscreening reduserer tarmkreftinsidens- og mortalitet litt, mens screening med gFOBT reduserte tarmkreftmortalitet litt, uten å påvirke tarmkreftinsidens. Effekten av sigmoidoskopiscreening var større hos menn enn kvinner. Sekundæranalysen av NORCCAP-studien inkluderte 163 personer med intervallkreft og 1740 personer med kreft i kontrollgruppen. Tarmkreftspesifikk mortalitet og totalmortalitet var lik i gruppene. Kohorten av personer som har fått et adenom fjernet inkluderte 40,293 personer. Sammenlignet med den generelle kvinnelige og mannlige befolkningen, var tarmkreftinsidens økt både blant kvinner og menn som hadde fått et adenom fjernet, men økningen var mer uttalt blant kvinner enn menn. Tarmkreftspesifikk mortalitet etter adenomfjerning var økt blant kvinner og redusert blant menn, sammenlignet med den generelle kvinnelige og mannlige befolkningen.

Fortolkning

Vi fant at tarmkreftscreening med gFOBT og sigmoidoskopi hadde en langtidsvarende effekt i minst 15 år. Personer som fikk intervallkreft etter en negativ screeningtest, hadde lik prognose som klinisk oppdaget kreft. Både sigmoidoskopiscreening og adenomfjerning har mindre effekt blant kvinner enn menn, og man bør vurdere kjønnsspesifikke retningslinjer for screening og adenomovervåkning.

3 Articles in the Thesis

Paper I:

Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis

Henriette C. Jodal, Lise M. Helsingen, Joseph C. Anderson, Lyubov Lytvyn, Per Olav Vandvik, Louise Emilsson

BMJ Open 2019;9:e032773

Paper II:

Mortality From Postscreening (Interval) Colorectal Cancers Is Comparable to That From Cancer in Unscreened Patients - A Randomized Sigmoidoscopy Trial

Henriette C. Jodal, Magnus Løberg, Øyvind Holme, Hans-Olov Adami, Michael Bretthauer, Louise Emilsson, David F. Ransohoff, Geir Hoff, Mette Kalager

Gastroenterology 2018;155:1787–1794

Paper III:

Long-Term Colorectal Cancer Incidence and Mortality for Women and Men

Henriette C. Jodal, Dagmar Klotz, Magnhild Herfindal, Ishita Barua, Petter Tag, Lise M. Helsingen, Erle Refsum, Øyvind Holme, Hans-Olov Adami, Michael Bretthauer, Mette Kalager, Magnus Løberg

In submission.

4 Background

4.1 Colorectal cancer epidemiology

Colorectal cancer is a major health burden. Worldwide, more than 1.9 million individuals are diagnosed with colorectal cancer each year, and 900,000 individuals die from colorectal cancer.[1] This makes colorectal cancer the third most common cancer form, and the cancer form responsible for the second most deaths. The cumulative risk of developing colorectal cancer before 85 years of age is 2.7% for men, and 1.8% for women worldwide.

In Norway, approximately 3500 individuals are diagnosed with colorectal cancer each year, and 650 individuals die from colorectal cancer.[2] The age-standardised incidence rate of colorectal cancer has increased three-fold in Norway since the Cancer Registry was established in 1951, and Norway now has one of the world's highest rates of colorectal cancer, with a cumulative risk before 75 years of age of 5.0% for men and 4.0% for women. [3] The cumulative risk of colorectal cancer death, on the other hand, increased from 1961 to approximately 1990, and has since receded to 1960-levels around 1%.[2] It is not known which factors are responsible for the increase in age-standardised rates of colorectal cancer seen among Norwegian women and men since the 1950s.

Globally, the highest incidence rates are in the Western world: Australia, New Zealand, Europe and North America, while the lowest rates are found in Africa and South-Central Asia.[1] How much of the observed difference between countries and regions that is due to diagnostic intensity, and how much is due to difference in true cancer risk, is unknown. The difference in risk of colorectal cancer may also be attributable to differences in life-style, and the increasing availability of colorectal cancer screening.

4.2 Colorectal cancer and life-style

Tobacco contains carcinogens, which cause genetic damage in several organs, including the colorectal mucosa. Tobacco smoking is the most well-documented life-style risk

factor of colorectal cancer.[4-6] Alcohol intake is also thought to be a risk factor of colorectal cancer; however, the evidence is not as convincing. In a meta-analysis of 15 studies assessing alcohol intake and colorectal cancer,[6] the authors found that the even though the pooled estimate showed an increased risk among individuals with higher alcohol intake, the largest studies showed no increased risk.

Body mass index (BMI) has in many studies been shown to be associated with colorectal cancer risk, however the increase in risk is small.[7-9] The pathogenesis behind this association is unknown. Some have suggested that the increased risk of colorectal cancer with higher BMI is due to diet, where consumption of red meat has shown the most convincing effect.[6 10 11] In addition, some studies suggest that healthy diets, with high intake of dietary fibre, fruit and vegetables decreases the risk of colorectal cancer.[12]

Lastly, anti-inflammatory medications, such as aspirin and non-steroidal inflammatory drugs (NSAIDs) may protect against colorectal cancer.[13-15] Aspirin may also promote an antitumourigenic effect through inhibition of platelet aggregation.[14]

4.3 Colorectal adenomas

Colorectal cancer develops from normal intestinal mucosa in a multistep process involving multiple genetic changes. Benign precursor lesions to colorectal cancer, i.e., polyps, may often be identified. These lesions may be pedunculated, sessile, flat, or depressed.[16] Often, they are visually recognised as wart-like outgrowths of the intestinal mucosa.

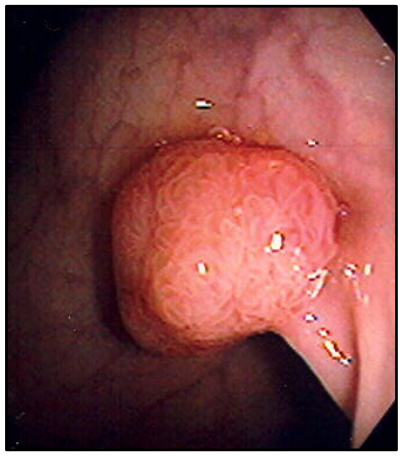

Figure 1: A stalked colorectal polyp. Attribute to Stephen Holland, M.D., Naperville Gastroenterology, Naperville, IL, USA.

The first recognised precursor lesion was colorectal adenomas, which are identified at histopathological examination of the polyp. The pathway from normal intestinal mucosa to colorectal cancer is known as the adenoma-carcinoma sequence.[17 18] Approximately 60-75% of all colorectal cancers are assumed to develop through the adenoma-carcinoma sequence.[19 20]

The time of transformation from a small adenoma to cancer is estimated to be approximately 5-15 years.[17 21 22] However, the majority of adenomas never develop into a colorectal cancer.

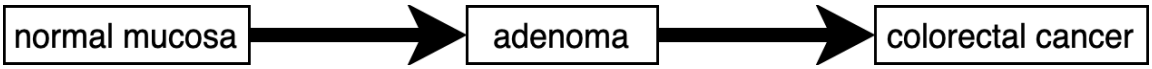

Figure 2: The adenoma-carcinoma sequence. Colorectal cancers develop from normal colorectal mucosa, through the dysplastic adenoma, and eventually to a carcinoma.

According to the morphology at histopathological examination, adenomas are subclassified as either tubular, tubulovillous or villous. Further, they are classified according to the grade of dysplasia: high or low.[16]

In recent decades, another precursor lesion to colorectal cancer, the serrated polyp, has been recognised. Serrated polyps includes hyperplastic polyps, sessile serrated lesions and traditional serrated adenomas.[16] The pathway from normal intestinal mucosa through a serrated polyp to colorectal cancer is known as the serrated pathway.[19] The cancers evolving from the different pathways may be genetically different.[16]

4.4 Diagnosis of colorectal adenomas and cancer

Colorectal cancer is rare among those younger than 40-50 years,[1 2] however after this age colorectal cancer should be expected in any individual with symptoms or findings such as stomach pain or unexplained anaemia. The initial test when colorectal cancer is suspected, but the suspicion is not very strong, is a test for occult (i.e., invisible) blood in a stool sample. If this test is positive, lower endoscopic procedures (i.e., rectoscopy, sigmoidoscopy and colonoscopy) is performed to confirm diagnosis and biopsy the lesion. If suspicion of colorectal cancer is stronger, endoscopy is the primary investigation.

4.4.1 Faecal occult blood test

Faecal occult blood tests (FOBT) are non-invasive and may be performed at home or in a general practitioner's office, and is therefore a simple tool to identify individuals who

may benefit from further investigation by endoscopy. The test, however, will be positive for any bleeding in the gastrointestinal tract, e.g., a gastric ulcer, diverticular disease or a bleeding colorectal cancer.

Larger, malignant lesions require more vascularity, and thus bleed more frequently than smaller, non-malignant lesions with less vascularity, as is also the case for cancers and adenomas.[23] Thus, FOBT has higher sensitivity for colorectal cancer than for adenomas. However, even with high vascularity, cancers do not bleed constantly, and the test may be a negative even though the individual has a cancer (a false negative).

4.4.1.1 Guaiac FOBT (gFOBT)

The eldest and mostly studied FOBT is guaiac FOBT (gFOBT). In gFOBT, the stool sample is applied to a piece of paper coated with guaiac (a phenolic compound extracted from wood resin of Guiacum trees), and fluid hydrogen peroxide is added. If haem, a component of red blood cells, is present, the guaiac turns blue within a few seconds. If it is not present, the change in colour will occur later. This test is not exclusive for human blood, thus dietary restrictions should be applied when performing the test.

Sensitivity, i.e., how often the test correctly identifies those with a disease, and specificity, i.e., how often the test correctly identifies those without a disease, may be adjusted by collecting stool samples from separate days. Mostly, three tests are required: while one out of three positive tests give high sensitivity and low specificity, three out of three positive test gives low sensitivity and high specificity. In screening programmes, the definition of a positive test may be adjusted for the positivity rate to match available colonoscopy resources, and varies from 1/12 (Croatia) to 5/6 (United Kingdom) positive samples.[24] Lastly, the sensitivity and specificity of the test varies widely with the brand of test, rehydration of the test material, and method of stool collection.

4.4.1.2 Faecal immunochemical test (FIT)

Over the past years, the faecal immunochemical test (FIT or iFOBT) has mostly replaced gFOBT. FIT is performed through the addition of an antibody against globin, another component of red blood cells, to a stool sample. FIT is, in contrast to gFOBT, specific to human blood. FIT measures the amount of haemoglobin in faeces, usually given as microgram haemoglobin per gram faeces. There is a small amount of physiological blood loss in stool even in healthy adults, thus a common positivity threshold for FIT is 20 microgram haemoglobin per gram faeces. As for gFOBT, however, the cut-off may be adjusted in order for the positivity rate to match the available colonoscopy resources in the country. In screening programmes, the positivity threshold varies from 15 to 80 microgram haemoglobin per gram faeces.[24]

4.4.2 Endoscopy

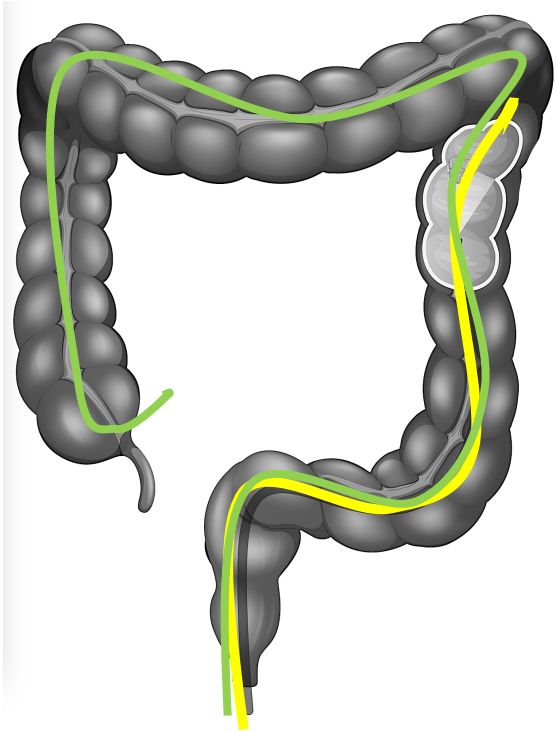

Figure 3: Endoscopy involves the visualisation of the mucosal lining of the colorectum. The reach of the sigmoidoscope is illustrated in yellow, the reach of the colonoscope in green. Illustration designed by brgfx/Freepik.

Lower endoscopic procedures include rectoscopy, sigmoidoscopy and colonoscopy. All three procedures are invasive, in contrast to FOBT, and involves visualisation of the mucosal lining of the whole or parts of colorectum. Rectoscopy, however, only visualises the rectum and distal parts of the sigmoid, and is rarely the first-choice as a diagnostic procedure for adenomas or colorectal cancer.

During endoscopy, both adenomas and colorectal cancer may be found, and adenomas removed. For individuals where the risk of colorectal cancer is considered to be high, it may be beneficial to perform endoscopy as a first-line investigation, rather than performing an FOBT first.

4.4.2.1 Sigmoidoscopy

In sigmoidoscopy, the lower parts of the colorectum are cleaned with an enema administered just before the procedure. During the procedure, the endoscopist can visualise the distal portions of the colorectum, in which 60% of the colorectal cancers occur:[25] the rectum, sigmoid, and parts of the descending colon. Even though sigmoidoscopy does not visualise the complete colorectum, it is considered a screening tool for the whole colorectum. Any finding of an adenoma or cancer at sigmoidoscopy, will be followed by a colonoscopy, as individuals with distal adenomas have a higher risk of synchronous proximal adenomas.[26]

4.4.2.2 Colonoscopy

Colonoscopy, on the other hand, involves the visualisation of the complete colorectum, and the distal parts of the ileum (small intestine). However, colonoscopy requires more preparation from the screened individual, as complete bowel cleansing including fasting is performed by the individual at home, starting the day before the colonoscopy.[27] For some individuals, this bowel cleansing is more burdensome than the colonoscopy itself.

4.4.3 Other diagnostic methods

In addition to FOBT and endoscopy, several different diagnostic methods have been developed, including detection of mutated or altered DNA known to be associated with colorectal cancer in faeces[28] and computer-tomographic (CT) colonography. However, the evidence for these methods is limited, and the gold standard today is considered to be colonoscopy.

4.5 Surveillance after adenoma removal

As most colorectal cancers develop from adenomas, individuals with adenomas are at increased risk of developing colorectal cancer. However, even after removal of the colorectal adenomas, the individual is still considered to be at increased risk of developing colorectal cancer: adenomas may have been missed or incompletely removed, and individuals with previous adenomas have a higher risk of adenoma recurrence.[29] Thus, individuals who have had adenomas removed are recommended to undergo colonoscopic surveillance to remove new adenomas and detect cancer pre-symptomatically, and thereby reduce colorectal cancer incidence and mortality.[30] Surveillance should only be offered to individuals with sufficiently high risk to expect a clinically significant benefit from surveillance, where the benefit of surveillance must by balanced against the harms of surveillance.[30] Thus, individuals who have had adenomas removed are stratified into colorectal cancer risk groups based on the characteristics of the removed adenomas. The recommended surveillance is dependent on the risk group.

4.5.1 Risk classification and surveillance recommendations

Traditionally, both European Society of Gastrointestinal Endoscopy (ESGE) and the US Multi-Society Task Force (USMSTF) on Colorectal Cancer have classified adenomas as advanced when size was ≥ 10 mm, or the adenomas had certain histological features: high-grade dysplasia, or ≥ 25% of villous growth pattern.[31 32] Non-advanced adenomas comprise none of these features. Individuals who had less than two non-advanced adenomas removed have been considered at low-risk for colorectal cancer. Individuals who had advanced adenomas removed, or who had more than three non-advanced adenomas removed, have been considered at high-risk for colorectal cancer, and thus recommended more frequent surveillance.

Recent evidence suggest that villous growth pattern is not associated with colorectal cancer risk.[33 34] Thus, in the 2020 update of the ESGE guidelines, growth pattern was not considered a risk criteria: According to the new ESGE guidelines, individuals with removal of 1-4 adenomas < 10 mm with low-grade dysplasia are considered low-risk, and

individuals with removal of adenomas ≥ 10 mm of size, or with high-grade dysplasia, or removal of ≥ 5 adenomas are considered high-risk.[35] The 2020 update of the guidelines from the USMSTF, on the other hand, does not change the risk classification.[36]

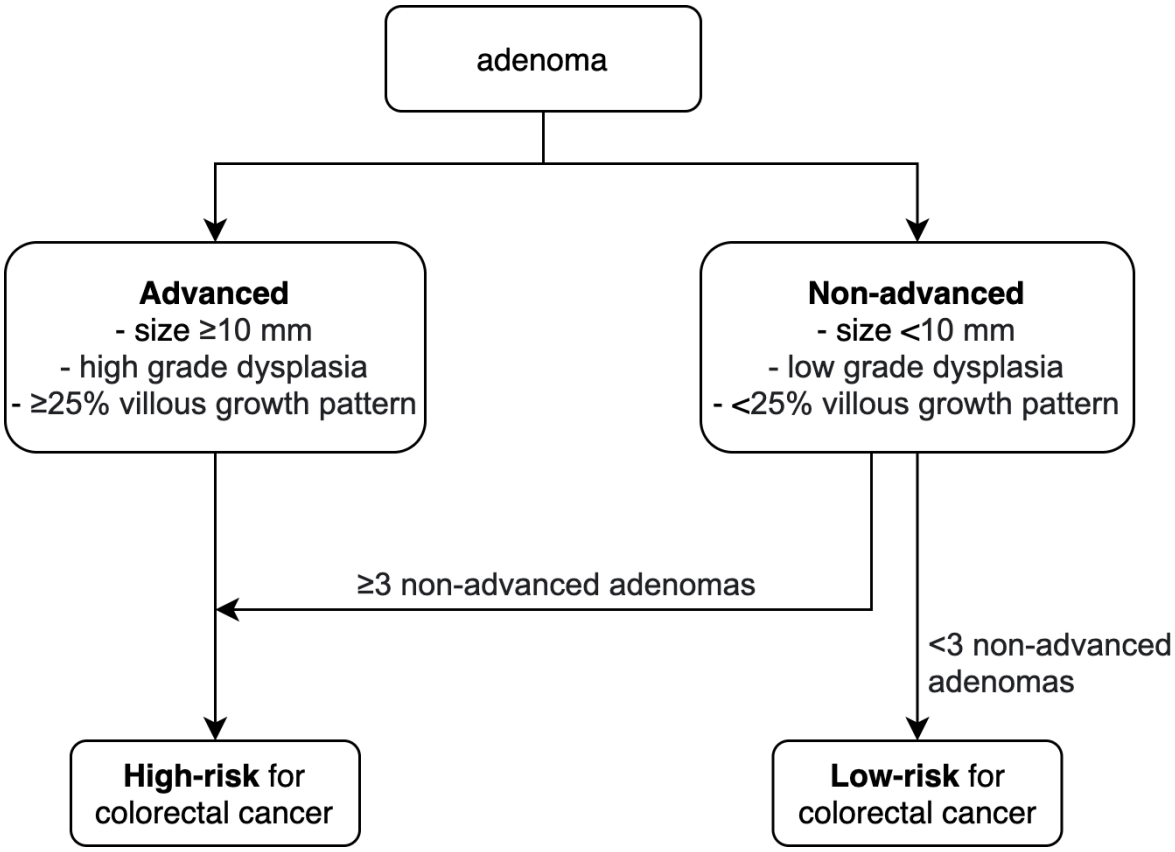

Figure 4: Adenomas have traditionally been classified into advanced and non-advanced adenomas, and depending on the presence of advanced and number of non-advanced adenomas have the individuals been classified as high- or low-risk for colorectal cancer.[31 32]

All mentioned guidelines recommend surveillance after seven to ten years for individuals with low-risk adenomas, and after three to five years for individuals with high-risk adenomas.[31 32 35 36]

4.6 Colorectal cancer screening

4.6.1 Principles of screening

Screening is performed in individuals who do not have recognised signs or symptoms of the condition it is being tested for.[37] The purpose of cancer screening is to identify a

group of individuals who have a higher risk of developing the cancer it is being screened for, or who have an early stage of the cancer.

Cancer screening aims at prevention and early detection of cancer to improve the outcomes of cancer incidence and mortality. However, screening involves medical testing of seemingly healthy individuals. Thus, introducing and continuing cancer screening should be carefully considered by weighing the benefits and harms. These benefits and harms may change with time, as knowledge and technology develop.

As early as in 1968 Wilson and Jungner identified ten principles for the World Health Organization, which may guide us when considering introducing and continuing cancer screening:[38]

1. The condition should be an important health problem.
2. There should be an accepted treatment for individuals with recognised disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognisable latent or early symptomatic phase.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including a diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuous process and not a “once and for all” project.

Frame 1: Wilson and Jungner's 10 principles of screening for disease.[38]

4.6.2 Sieve and sort: the screening test and work-up

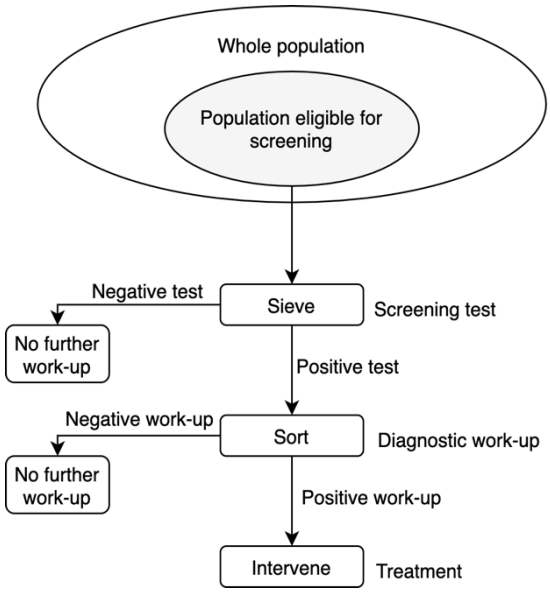

Figure 5: The screening test may be visualised as a sieve, where the eligible population is selected for further diagnostic-work-up.[37]

work-up by colonoscopy. If colonoscopy is used as the screening tool, however, the sieving and sorting processes are combined. Cancer screening may be considered as mainly preventive, early detection, or a mixture of the two.[39]

4.6.2.1 Preventive screening

Preventive screening relies on methods which identifies precursor lesions to the cancer, such as non-invasive neoplasia or dysplastic lesions.[39] Thus, preventive screening methods prevent the development of cancer by identifying lesions that may be treated before cancer develops, and thereby

The initial screening test may be visualised as a sieve, where individuals with a positive test will be offered diagnostic work-up.[37] After further diagnostic work-up (sorting), individuals who still are considered at risk, may be subject to an intervention. This combination of screening test and further work-up, defines a screening episode.

For colorectal cancer, both FOBT and lower endoscopy are used as screening tools. FOBT may represent the sieve, where individuals are chosen to further diagnostic

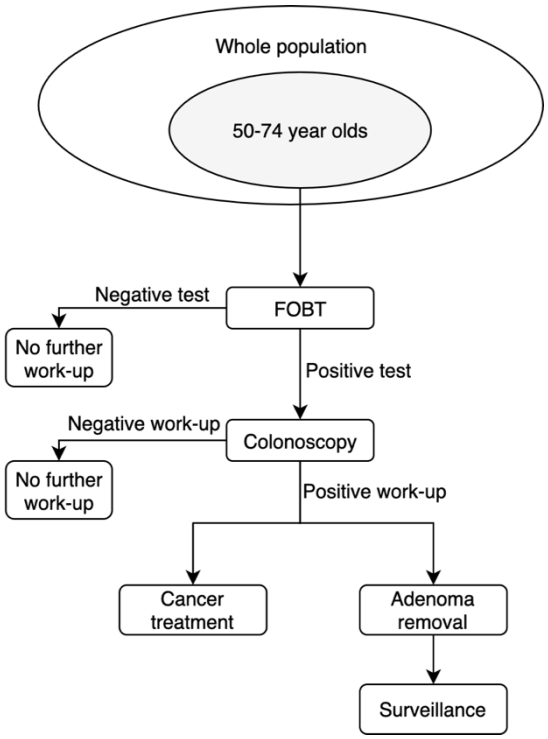

Figure 6: The screening process for colorectal cancer, inspired by Raffle et al[37]

reduce the incidence of cancer. Consequently, the mortality of cancer will also be reduced.

Sigmoidoscopy and colonoscopy are considered preventive screening tests for colorectal cancer: during both procedures, precursor lesions such as adenomas may be identified and removed. In addition, by identifying adenomas, the test will identify individuals considered at increased risk of developing new adenomas and colorectal cancer in the future. Serrated lesions may also be identified and treated by sigmoidoscopy and colonoscopy.

4.6.2.2 Early detection screening

Early detection screening relies on methods that detect cancers in early stages.[39] The rationale is to detect cancer at a curable stage. The prerequisite for early detection screening to be effective is that there is a cure for the cancer and that earlier diagnosis is more beneficial than later diagnosis. The aim of early detection screening is to reduce the cancer mortality by starting treatment before advanced stages of the cancer. Early detection screening, however, will not decrease the cancer incidence.

FOBT is considered an early detection screening test for colorectal cancer: FOBTs are positive for bleeding lesions only, and larger lesions with more vascularity, such as cancers, bleed more frequently.[23] However, FOBT may also identify some bleeding adenomas, and hence be considered a mixture of early detection and preventive screening.

4.6.2.3 Overdiagnosis

Early detection screening may increase the incidence of cancer: among those diagnosed, there are individuals with a cancer that would never have presented within the individual's lifetime: either because the cancer regressed spontaneously, or because growth of the cancer was so slow that it would not cause symptoms before the individual died of another reason.[40] [41] [42] These individuals are overdiagnosed. It is not possible to

distinguish the overdiagnosed cancers from the potential life-threatening cancers. Hence, everyone with the disease is treated, but there are no real benefits for those overdiagnosed.

Overdiagnosis of precursor lesions, such as adenomas, may also occur: the precursor lesions may, like the cancers, regress spontaneously or grow slowly.

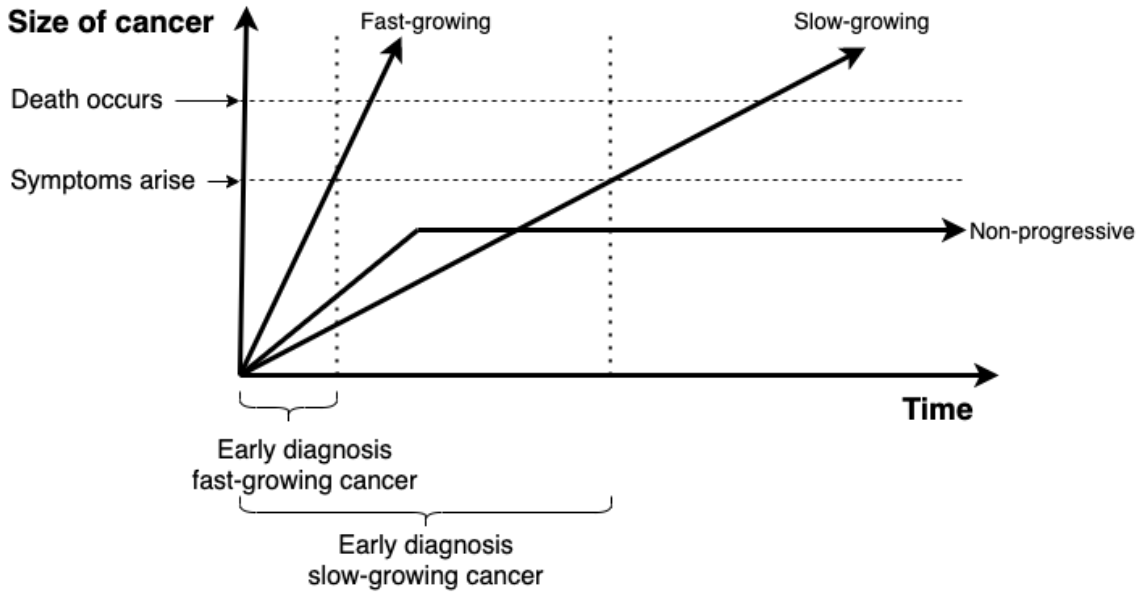

Figure 7: Cancers and precursor lesions may progress at different speeds. In this simplified figure,[40] all cancers grow rapidly, slowly or stop to progress. Early diagnosis before symptoms arise may occur due to screening. Any diagnosed cancer which never reach "symptoms arise" is an overdiagnosed cancer, in this case this is only the non-progressive cancer.

4.6.3 The intervention: treatment and surveillance

Screening is a process: the benefits and burdens of the screening test, diagnostic work-up, treatment and surveillance must be considered when accepting screening, both for the individual, and the society in which screening is offered.

A screening test may have several different outcomes:

1. Negative screening test
    a. True negative (i.e., healthy individuals)

b. False negative (i.e., thought to be healthy individuals, but are truly at risk or sick)

2. Those with a positive screening test
    a. True positive (i.e., sick individuals)
    b. False positive (i.e., thought to be individuals at risk or sick, but are truly healthy)

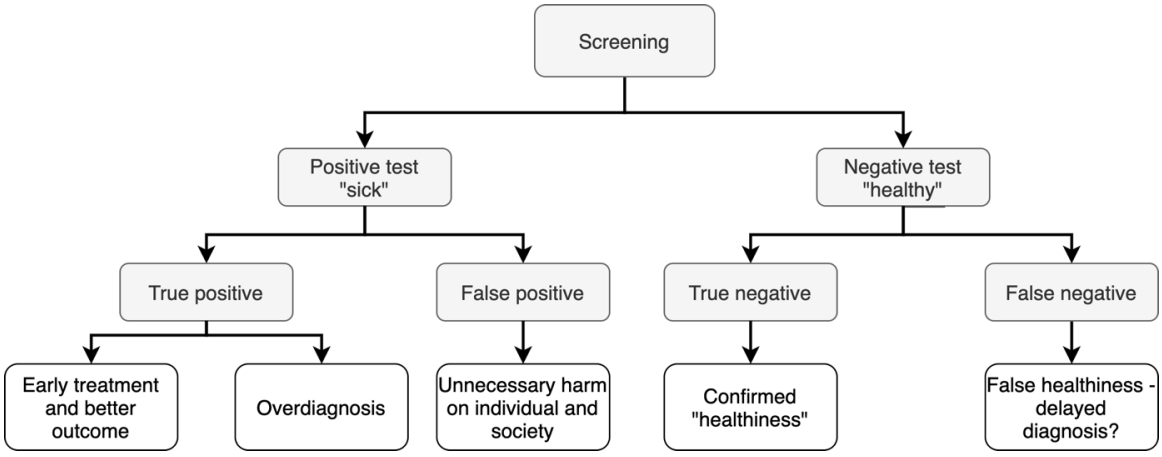

Figure 8: Overview of the different groups . The true positives leading to early diagnosis and better outcome, as well as those who are confirmed "healthy" are the ones usually remembered when discussing screening.

For individuals with a positive screening test, further work-up and possibly treatment as well as surveillance will follow: an individual with a positive screening FOBT will be recommended further work-up by colonoscopy (a complete screening episode), and possibly adenoma or cancer treatment, as well as surveillance (a year-long screening process). Among the positives, however, there are both true and false positive tests. It is assumed that individuals with a true positive test will benefit from the screening, as they are identified as individuals at risk (adenoma) or diagnosed at an earlier stage (cancer). The true positives, however, are a mixture of individuals who will benefit from the treatment, and the overdiagnosed.

Further, individuals with a false positive test will not benefit from further work-up. However, if the test is identified as a false positive during work-up, before treatment, the harm will be limited.

For individuals with a negative screening test, the screening episode ends; there is no work-up, no treatment, nor surveillance. However, false negative tests occur occasionally.

Interval cancers

Cancers detected by symptoms or clinical findings after a negative screening episode, but before the next screening episode, are known as interval cancers.

At screening, colorectal cancers may be missed by the FOBT as the cancer does only bleed intermittently, or missed at endoscopy due to low adenoma detection rate (ADR) (a false negative test). In addition, lesions found at endoscopy may be incompletely resected, and the remains may give rise to a cancer. Lastly, completely new lesions may also develop rapidly into a cancer between two screening episodes.

Thus, interval cancers comprise three different entities (missed, incompletely resected, and new lesions), which we cannot distinguish clinically.

The new lesions that arise between screening episodes are known as the "true" interval cancers. These lesions grow faster than the average cancer, and their occurrence cannot be affected by the performance of the screening tests. The frequency of cancers arising from missed lesions, on the other hand, may be affected by increasing the sensitivity of the screening, e.g., by repeating FOBT annually or biennially. The frequency of cancers arising from incompletely resected lesions may be affected by training of the endoscopists. The "true" interval cancers are thought to be more aggressive, due to their fast growth.

4.7 Colorectal cancer screening and surveillance research in Norway

Norway has a public, single-payer healthcare system with universal coverage. All residents are assigned an individually unique national registration number, through which residents can be identified in national registries and hospital databases. The Cancer Registry of Norway is close to 100% complete.[43] Currently, colorectal cancer screening is not available in Norway, but is planned to be implemented late 2021.[44] In addition to

having one of the highest colorectal cancer incidences in the world, this makes Norway ideal for colorectal cancer research. Indeed, Norway participates in several of the large colorectal cancer screening and surveillance trials.

4.7.1 Colorectal cancer screening effect studies

Internationally, there are four large-scale randomised controlled trials (RCTs) on the effect of sigmoidoscopy screening on colorectal cancer incidence and mortality.[45-48] One of these are the NORwegian Colorectal CAncer Prevention (NORCCAP) trial (ClinicalTrials.gov: NCT00119912),[45] where 20,780 individuals aged 50-64 years were randomised to sigmoidoscopy screening, and 79,430 to a control group with no intervention. The trial intervention was performed in the years 1999 through 2001. At this time, screening was not available in Norway, thus the control group was screening-naïve.

Presently, Norway is also participating in the Nordic-European Initiative on Colorectal Cancer (NordICC) trial (ClinicalTrials.gov: NCT00883792),[49] which investigates the effect of colonoscopy screening on colorectal cancer incidence and mortality among individuals aged 55-64 years, compared to no intervention. This is one of three major, international, ongoing RCTs on this subject,[49-51] none of which yet have long enough follow-up to evaluate the endpoints.

4.7.2 Colorectal cancer screening programme pilot

In 2012 Norway established a pilot for a national colorectal cancer screening programme. In the pilot programme, individuals aged 50-74 years were randomly assigned in a 1:1 ratio to either up to four rounds of biennial FIT or a once-only sigmoidoscopy screening (ClinicalTrials.gov: NCT01538550).[52] FIT screening was performed by a single stool kit sent to the invited individual and returned by mail. Any individual with a negative FIT screening or who failed to return their test kit, was re-invited in the next screening round two years later. The sigmoidoscopy screening was performed at two dedicated centres by gastroenterology residents who were intensively trained. A positive sigmoidoscopy was defined according to the traditional high-risk criteria of ESGE 2013,[31] i.e., ≥ 3 adenomas,

any adenoma ≥ 10 mm in size, or with high-grade dysplasia, or with villous growth pattern. Any positive screening test was scheduled to subsequent investigation by colonoscopy. In total, 139,291 individuals were included and randomised, 69,125 in the FIT group and 70,096 in the sigmoidoscopy group.

The primary aim of the pilot programme was to compare the long-term effectiveness of FIT and sigmoidoscopy screening on colorectal cancer incidence and mortality, and the inclusion was completed in 2019. Baseline results show that both repetitive FIT and sigmoidoscopy are feasible screening methods, however FIT had higher participation (68.4% vs 52.1% for sigmoidoscopy), while adverse effects of the two screening methods were the same.[52] Results on the effect on colorectal cancer incidence and mortality is not expected until 10 years of follow-up.

After the positive results from the national screening pilot programme, it has been decided to implement an organised population screening programme for colorectal cancer in Norway, with the first invitations being sent out late 2021. In the screening programme, five biennial rounds of FIT will be offered. Only individuals who turn 55 years old in the year of invitation will be invited, i.e., any individual who is older than 55 years will not be offered screening. When resources in terms of structure, personnel and trained endoscopists are strengthened, it is planned a gradual implementation of a once-only colonoscopy as the primary screening procedure.[44]

4.7.3 Adenoma surveillance effect studies

Internationally, only two RCTs have been performed to investigate the optimal surveillance interval after adenoma removal by investigating the effect on colorectal cancer incidence and mortality.[53] [54] The first included less than 1000 individuals who had adenomas removed between 1981 and 1991.[53] The second is the European Polyp Surveillance (EPoS) study(ClinicalTrials.gov: NCT02319928), which Norway is participating in.[54] In this study, individuals who have had low-risk adenomas removed, are randomised to surveillance either after 5 years or after 10 years. Individuals who have had high-risk adenomas removed are randomised to surveillance after 3 or 5 years. The

study just finished recruiting 20,000 individuals, and follow-up is planned to continue until around year 2030.

5 Thesis Aims

The aims of this thesis are

1. To investigate the long-term colorectal cancer incidence and mortality after colorectal cancer screening.
2. To investigate the long-term colorectal cancer mortality of colorectal interval cancers.
3. To investigate the long-term colorectal cancer incidence and mortality after adenoma removal.

6 Materials and Methods

6.1 BMJ Rapid Recommendation: Systematic review and network meta-analysis

The process of summarising new knowledge into clinical guidelines may take years. Therefore, the British Medical Journal (BMJ) and the non-profit foundation MAGIC collaborate to rapidly respond to practice changing evidence, summarise the available evidence and provide new guidelines.[55] In this process, meta-analyses of available knowledge are required.

In response to new results from three major sigmoidoscopy screening trials, with approximately 15 years follow-up,[56-58] new guidelines for colorectal cancer screening were requested.[59] A guideline panel was established, consisting of patient partners (individuals with experience from colorectal cancer), general practitioners, general internists, gastroenterologists, content experts on colorectal cancer screening, methodologists, and a nurse practitioner. To summarise the available evidence on colorectal cancer screening, a network meta-analysis (NMA) was requested, which is included as Paper I of this thesis.

The protocol of the systematic review was registered with PROSPERO (CRD42018093401).

6.1.1 Study aim

The aim of the NMA was to compare colorectal cancer incidence and mortality, as well as all-cause mortality, of individuals who had been screened for colorectal cancer using faecal tests, sigmoidoscopy or colonoscopy, in a 15-year perspective after initial screening. In addition, the aim was to analyse the same outcomes among women and men separately. Lastly, the aim was to compare other patient-important outcomes among the screened individuals, as decided *a priori* by the guideline panel.

6.1.2 Study population

The panel requested evidence on healthy individuals aged 50-79 years participating in RCTs on colorectal cancer screening, as this is the population who are commonly considered eligible for screening programmes.[24 60] Evidence including only high-risk individuals, such as individuals with inflammatory bowel disease, familial polyposis syndrome or hereditary non-polyposis colorectal cancer (Lynch) syndrome was excluded.

6.1.3 Study intervention

The panel requested evidence from RCTs on one or more of the screening methods:

1. Sigmoidoscopy screening, once-only
2. Colorectal cancer screening, once-only
3. gFOBT, annually or biennially
4. FIT, annually or biennially

The comparator was one of the other screening methods, or no screening.

The primary outcome of the RCT had to be colorectal cancer incidence or mortality. For these outcomes to be included in the meta-analysis, follow-up had to be at least 5 years,

as previous meta-analyses have shown that it takes at least 5 years after screening until an effect on colorectal cancer incidence and mortality can be observed.[61 62]

Secondary outcomes of interest were bleeding, perforation, screening-related death, other major and minor complications, need for further diagnostic work-up, procedure-related pain, psychological impact of a positive test, and absence from work to in relation to the screening test. These outcomes occur immediately or soon after screening, therefore no follow-up was required.

6.1.4 Data extraction and rating of evidence

We updated a previously performed search from a published Cochrane systematic review on colorectal cancer screening.[63] The search was extended from November 2012 to December 2018. Two reviewers independently screened titles, abstracts and full texts for trials fulfilling the eligibility criteria. Two reviewers independently extracted data to a standardised form. Risk of bias was evaluated by two independent reviewers using the modified version of the Cochrane tool, as this approach has been shown to enhance the validity and reliability of the risk of bias evaluation.[64] Consensus was reached at all levels.

Certainty of evidence of estimates was graded according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[65] We rated direct, indirect and NMA estimates separately. We used the lower certainty rating of the two pairwise estimates for indirect comparisons, and evaluated the coherence of the direct and indirect ratings for NMA estimates.[66] For harms and burdens, we used the GRADE for assessment of evidence about prognosis.[67]

6.1.5 Ethical approval

No ethical approval was needed, as this study is summarising already published evidence.

6.2 The NORwegian Colorectal CAncer Prevention trial

Paper II of this thesis is based on the NORCCAP trial (ClinicalTrials.gov: NCT00119912).[45]

6.2.1 Study aim

The aim of the NORCCAP trial was to estimate the effectiveness of sigmoidoscopy screening on colorectal cancer incidence and mortality in a population-based screening trial. In this thesis, a secondary analysis of the NORCCAP trial is included as Paper II. The aim of this analysis was to compare colorectal cancer mortality and all-cause mortality of individuals with interval colorectal cancers after sigmoidoscopy, to colorectal cancer mortality and all-cause mortality of non-screened individuals.

6.2.2 Study population

NORCCAP is a randomised controlled trial. Participants in the trial included all women and men aged 50-64 years living in the city of Oslo and Telemark County in 1998. The women and men were identified through the Norwegian Population Registry. Equal numbers of women and men were randomly sampled, and invited to screening by mail (screening arm). Individuals in the screening arm was further randomised 1:1 into a group that was offered once-only sigmoidoscopy only, and a group that was offered a combination of once-only FIT and sigmoidoscopy. Those who were not included in the screening arm (the remaining inhabitants of the same age in the capture areas) were never contacted nor offered any intervention outside standard health care, and constituted the control arm. Screening took place in 1999 through 2001.

The only exclusion criteria from participation in the trial was a history of colorectal cancer before study entry date.

6.2.3 Study intervention

All screening participants were screened at three dedicated screening centres, at which they received an enema for bowel cleansing upon attendance, before sigmoidoscopy was performed. At sigmoidoscopy all visible lesions were biopsied and sent to histopathological evaluation. Screening participants who were randomised to the sigmoidoscopy and FIT combination group, brought a faecal sample to the screening centre, which was analysed before sigmoidoscopy was performed.

A positive screening test was defined as a polyp with diameter 10 mm or greater (regardless of histology), any adenoma, colorectal cancer, or a positive FIT. All individuals with a positive screening test were referred for a colonoscopy within four weeks at the same screening centres. Surveillance was recommended according to the Norwegian guidelines that were in place at the time of inclusion.[68]

Individuals in the control arm were not informed about the screening study and received standard care. During the period the trial took place and participants were followed, colorectal cancer screening was not available for the population outside the screening arm of the trial.

6.2.4 Analysis

Paper II does not include the primary analysis of the NORCCAP study (i.e., comparison of colorectal cancer incidence and mortality in the screening and control arms). In Paper II, we compared colorectal cancer mortality and all-cause mortality between two groups:

1) The interval cancer group: Individuals in the screening arm who complied to screening and later developed colorectal cancer (i.e., excluding cancers diagnosed at screening and cancers in the non-compliers group).
2) The control group: Individuals in the control arm who were diagnosed with colorectal cancer.

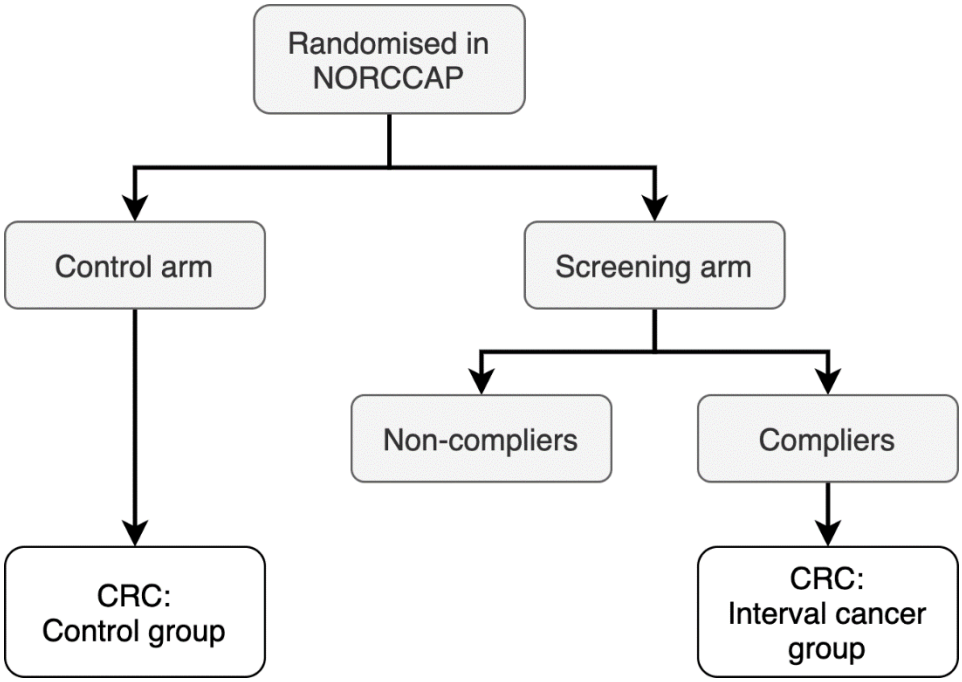

Figure 9: Flow chart of the NORCCAP trial. The grey boxes are parts of the original trial. The white boxes are the comparison groups studied in Paper II of this thesis.

Time of inclusion in this analysis was date of colorectal cancer diagnosis.

6.2.5 Ethical approval

The NORCCAP trial was approved by the Norwegian Data Protection Authority (98/1408-2) and the Regional Ethics Committee of South-Eastern Norway (2010/3087). All compliers of the screening arm provided written informed consent at the time of screening intervention.

6.3 The Surveillance after Adenoma Removal study

Paper III of this thesis is based on the Surveillance after Adenoma Removal (SAR) cohort study.

6.3.1 Study aim

The aim of this study was to evaluate the long-term colorectal cancer incidence and mortality of individuals who have had colorectal adenomas removed.

6.3.2 Study population

The study population was identified through the Cancer Registry of Norway, and comprised all individuals 40 years or older who had colorectal adenomas removed in the period 1993-2007 (cohort). Individuals were identified by topographical ICD-O-3 codes 180, 182 through 189, 199, or 209, combined with morphological ICD-O-3 codes 8140, 8210, 8211, 8261, or 8263. All adenomas reported to the Cancer Registry more than four months apart were recorded as separate occurrences.[69] We pooled all adenoma reports within the same occurrence and classified the individual according to the most severe characteristic. Individuals who had prior colorectal cancer or familial polyposis syndrome (identified through the polyposis registry of the Cancer Registry) were excluded.

6.3.3 Cohort study

The cohort was followed through linkage with the Cancer Registry, the Cause of Death Registry and the Norwegian Population Registry, from time of first adenoma, through 31st December 2018. The general population, matched on age and being cancer-free at the time of first adenoma removal, was used as control group.

The primary endpoints of the study were colorectal cancer incidence and mortality.

6.3.4 Chart review study

For the chart review, we randomly selected a subcohort comprising 1100 individuals from the full cohort living in 10 counties in Norway. The counties were chosen on basis of practicalities around traveling to perform the chart review, as well as to ensure geographical variation.

Chart review was performed from summer 2017 through autumn 2018.

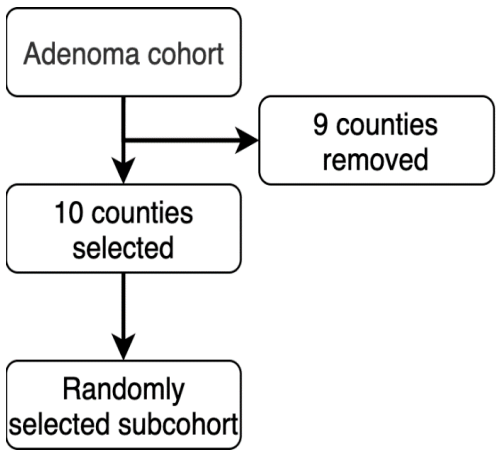

Figure 10: Flow chart of the selection of the subcohort for chart review.

6.3.5 Ethical approval

The SAR study was approved by the Regional Ethics Committee of South-Eastern Norway (2014/2352). Informed consent for patients included in the cohort study was waived due to its registry-based design. All living individuals sampled for chart review were provided with written information about the study, and were given the opportunity to opt out from the chart review.

6.4 Statistical methods

Stata version 14.1, 15.1 and 16.1 (StataCorp, College Station, TX, USA) were used for all analyses, except Gray's test, which was performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

6.4.1 Network meta-analysis

6.4.1.1 Fixed-effects versus random-effects

Meta-analyses may be performed using one of two main methods: fixed-effects or random-effects modelling. The choice of method depends upon the underlying assumptions.

The fixed-effects model assumes that the every included study have a common true effect size.[70] E.g., if the same FOBT trial is performed in different countries, but with same inclusion and exclusion criteria, the same brand of FOBT and the same definition of a positive test, one may assume that these trials measure the same true underlying effect size. The varying effect estimates in each study are only due to natural statistical variation. The pooled estimate will have a narrower confidence interval than each separate trial.

The random-effects model, on the other hand, assumes that every included study have different true underlying effect sizes.[70] These effect sizes are distributed around a mean. E.g., if the FOBT trials have slight differences in inclusion or exclusion criteria, brand of FOBT or definition of a positive test, each trial will estimate different true effects, which

will be normally distributed. The varying estimates between the studies will be due to both varying true estimates, and natural statistical variation. The pooled estimate of the random-effect meta-analysis will be an average effect of the measured effect in each study. As the true estimates vary between the included studies, the confidence interval will be greater in random-effects than in fixed-effects model.

In Paper I, the pooled studies were slightly different with regards to inclusion and exclusion criteria, brand of FOBT test, and definition of a positive test for both FOBT and sigmoidoscopy. Thus, we chose to perform a random-effects meta-analysis.

6.4.1.2 Heterogeneity

In a random-effects model, there are two sources of overall study error variance: the within-study and between-study variance.[70] The observed effect in a study may differ from the true effect of that study, due to random variability. This is known as the within-study variance, and is also present in fixed-effects models. In addition, the true effect of any study may differ from the true mean effect, i.e., the pooled estimate of all the studies. This is known as the between-study variance.

The standard deviation of the distribution of between-study variances is called τ (tau), and the variance τ^2. This variance is common to all studies of the random-effects meta-analysis. The heterogeneity estimator τ^2 may be estimated from the data by several different methods. In Paper I, we chose to use the restricted maximum likelihood (REML)

method. This method is preferable when the heterogeneity is large, included studies are small, or outcomes are rare.[71]

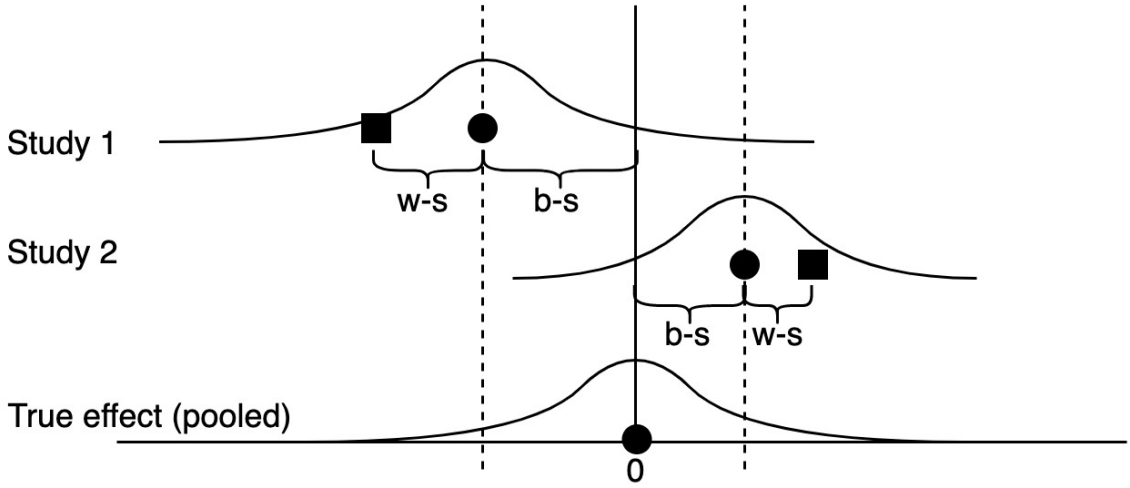

Figure 11: Illustration of variance in a random-effects model. Filled square: observed value of a study. Filled circle: true value of a study B-s: between-study variance. W-s: Within-study variance. 0: true pooled effect.[70]

6.4.1.3 Subgroup analysis

Comparing subgroups, such as sex, may be subject to several biases. In our analysis, we have chosen to explore the effect modification of sex, as requested by the guideline panel, by using a one-stage multilevel meta-regression model.[72] [73] This model is commonly used, however subject to bias, as it combines both within-study and between-study relationships. Thus, we also explored the subgroups by applying the *deft* approach.[73] In the *deft* approach, the mean difference in treatment effect between the subgroups, e.g., the women and men, in each trial is calculated. Then, a meta-analysis is performed, summarising the mean differences in each study. Using this approach, between-study relationships are accounted for, and only within-study interactions studied.

6.4.2 Survival analysis

To account for the time at which an event (e.g., colorectal cancer incidence or mortality) occurs, we used survival analysis. Survival analysis is of particular usefulness when follow-up time differs between groups being compared. For instance, if all deaths occur within the first month in the study population, but within the first year in the reference

population, the mortality ratio comparing the first year would be 1, even though the individuals in the two groups have different follow-up time. The time at which the events occur is not considered. Survival analysis is used in both Paper II and Paper III.

6.4.2.1 Competing risks

When following a group of individuals over time, such as in an RCT or observational study, not all individuals will be followed to an event of interest or to the end of the study period. A competing risk may occur. A competing risk is an event which will prevent the event of interest from occurring, e.g., any other death than colorectal cancer-specific death will prevent the event of colorectal cancer death, as death may only occur once.[74] For colorectal cancer incidence, any death is a competing risk. Competing risks may be treated in different ways in analysis.

6.4.2.2 Cumulative incidence

Survival times are often described as cause-specific survival functions, e.g., Kaplan-Meier curves. In these methods, individuals experiencing competing risks are censored, and treated as if they could experience the event of interest in the future. The true number of individuals observed is smaller. However, the remaining individuals represent those censored, in addition to themselves, i.e., are weighted up.[74] This is informative when looking at the risk of cause-specific death in hindsight and with a public perspective: what was the risk of dying from colorectal cancer for the group of individuals who had an adenoma removed? However, for the individual who wonders what his or her risk of colorectal cancer death after adenoma removal is, it will overestimate the risk.

In Paper III, we chose to use a cumulative incidence function to graphically present the time-to-event, since we wanted to underline the forward-looking aspect of the individual who has had an adenoma removed. Using the cumulative incidence function, individuals experiencing competing risks will no longer be at risk for the event of interest, but will still be considered observed. Thus, there is no change in weight of the remaining individuals.[74] The cumulative incidence curve therefore answers the question about the

probability of dying from colorectal cancer for of the individual who have just had an adenoma removed. This measure is independent of the incidence of competing risks.

6.4.2.3 Cox proportional hazard regression

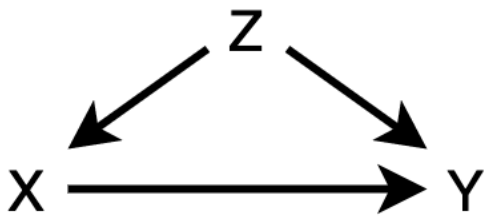

Figure 12: Directed acyclic graph showing the correlation between the independent variable X and the dependent variable Y, confounded by Z.

The effect of one or more predictor (independent) variables (X) on survival time until a specified outcome (dependent) variable (Y) occurs may be investigated using regression analysis. In multiple regression, confounding variables (Z), which may affect both the dependent and the independent variable, may be accounted for by adding this as a covariate (an additional independent variable).

In an RCT, the intervention and control groups are exchangeable at the time of randomisation, i.e., similar in all ways, and the only difference is the intervention of interest. Thus, a comparison between the two groups will measure the effect of the intervention (independent variable), and establish a causal relationship. In observational studies, on the other hand, we do not know whether the groups are exchangeable: there may be unmeasured confounding factors present. Thus, regression analysis of observational studies does not measure the effect unless no residual confounding is assumed, but may establish a correlational relationship between the dependent and independent variable.

In Paper II and III, Cox proportional hazard regression models were applied. Cox models assume that the hazard ratio is proportional in the two groups throughout the study period. This is not the case in our studies. However, the hazard ratio can also be interpreted as the average hazard ratio for the whole study period, i.e., a measure of the relative risk.[75]

In Paper II, the Cox model was applied to provide sex- and age-adjusted estimates of the hazard ratio of colorectal cancer mortality and all-cause mortality for interval cancers

compared to the cancers in the control group. In Paper III, the Cox model provides the hazard ratio of colorectal cancer incidence and mortality in individuals with adenomas, adjusted for several different covariates (e.g., sex, age group, characteristics of adenoma).

6.4.3 Incidence and mortality ratios

6.4.3.1 Standardised ratios

Standardised ratios compare the observed number of events (O) (e.g., number of colorectal cancer cases) in the study population to expected number of events (E) in a similar reference population, e.g., an age- and sex-matched population. The standardised ratio thus describes whether the event of interest is more common in the study population than in the reference population.

In Paper III, the reference population was matched to the study population based on age and sex. For each sex- and age-stratum, a stratum-specific person-time (T) was available from the study population, and the number of events for the same person-time for each stratum was applied from the reference population.

$$\frac{O/T}{E/T} = \frac{O}{E}$$

The standardisation ensures that the populations being compared are similar. If crude non-standardised numbers were used, the age- and sex-distribution of the study population and reference population would probably be different, e.g., because adenomas are more common among elderly than among younger individuals, and thus our comparison group would not have been valid.

In Paper III of this thesis, standardised mortality ratios provide a relative and absolute comparison of risk of colorectal cancer mortality to the general population. This is in contrast to the Cox proportional hazard regression model, in which the comparison is relative to other individuals with adenomas.

6.4.3.2 Incidence-based mortality ratios

Even though the mortality rates are standardised on variables such as age and sex, the two compared groups may differ in when diagnosis was established.

In Paper III, follow-up of the individuals who had adenomas removed started after the adenoma had been detected and removed. At the time of adenoma removal, they had also been confirmed free of colorectal cancers. Thus, all colorectal cancers that were included in the analysis among individuals who had an adenoma removed were diagnosed after the date of adenoma removal. Individuals from the general population, on the other hand, may have both diagnosed and undiagnosed colorectal cancers at the same point in time. Hence, comparing the standardised colorectal cancer mortality rate among individuals who have had adenomas removed, to standardised colorectal cancer mortality rates among the general population, the effect of the adenoma removal would be overestimated.

When using incidence-based mortality ratios, however, the reference population is matched to the study population based on time of incidence.[76] Thus, in Paper III, only individuals who did not have a diagnosis of colorectal cancer at the time of inclusion (which corresponds to the removal of first adenoma in the adenoma group) were enrolled in the matched reference population. The incidence-based mortality estimates thus eliminates any difference between the groups due to already diagnosed cancer. However, individuals in the reference population still have a higher probability of an undiagnosed colorectal cancer at the time of enrolment since they have not had a colorectal examination. The incidence-based mortality ratio is similar to the measure you obtain in RCTs, where individuals with a previous cancer diagnosis is normally excluded, but where you also often have less information about control group participants.

6.4.4 Absolute vs relative measures

All methods described above, generate relative estimates. A relative increase of a high-prevalent disease, translate into a high absolute increase. The same relative increase of a low-prevalent disease, however, translates into a low absolute increase.

Suppose removing a colorectal adenoma reduces the risk of colorectal cancer by 20% (relative reduction). The absolute risk reduction depends on the risk for an individual without the intervention: if the risk of developing cancer was 30 in 1000 before adenoma removal, the absolute risk reduction would be $30 \times 20\% = 6$ fewer colorectal cancer cases per 1000 such individuals who had adenomas removed. However, if the risk before adenoma removal was 10 in 1000, the same 20% relative risk reduction would translate into $10 \times 20\% = 2$ fewer colorectal cancer cases per 1000 such individuals who have adenomas removed. While the relative risk remains the same, the absolute risk changes dependent on the background risk. The change in absolute risk depends on the prevalence of disease.

This illustrates the importance of evaluating absolute measures in decision-making, both for the individual and the public. It is tempting to put all efforts into decreasing the relative risk of disease by 20%, no matter the cost. However, if applying the absolute risk estimate, you may find diseases with smaller change in relative risk that change the life of more individuals, for the same cost. To make informed choices, both patients and caregivers need to be presented with absolute values of colorectal cancer risk.[30]

7 Summary of the Papers

7.1 Paper I

Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis. BMJ Open 2019;9:e032773

Our search yielded 8992 potentially relevant records. Eventually, 12 RCTs described in 36 articles were included in the systematic review: five RCTs on gFOBT screening, two

RCTs on FIT screening, five RCTs on sigmoidoscopy screening, and two RCTs on colonoscopy screening. The included trials enrolled a total of 1,325,618 participants, with follow-up ranging from zero to 30 years.

For RCTs with >5 years of follow-up, the requirement for analyses of colorectal cancer incidence and mortality, follow-up ranged from 10.5-30 years. However, in main analyses, reports including follow-up from 10.5-19.5 years was selected. These RCTs included four trials on gFOBT screening and four trials on sigmoidoscopy screening. No RCTs on FIT and colonoscopy had sufficient follow-up to be included in meta-analysis on colorectal cancer incidence and mortality. Only one report was assigned high risk of bias for the outcomes of colorectal cancer incidence and mortality.

Compared to no screening, we found high certainty evidence for sigmoidoscopy screening slightly reducing colorectal cancer incidence (relative risk (RR) 0.76, 95% confidence interval (CI) 0.70-0.83) and mortality (RR 0.74, 95% CI 0.69-0.80). We also found high certainty evidence that gFOBT screening had little or no difference on colorectal cancer incidence (annual: RR 0.86, 95% CI 0.72-1.03; biennial: RR 0.95, 95% CI 0.87-1.04), but slightly reduced colorectal cancer mortality (annual: RR 0.69, 95% CI 0.56-0.86; biennial: RR 0.88, 95% CI 0.82-0.93). We found high certainty evidence of a greater relative effect of sigmoidoscopy screening in men (incidence: RR 0.74, 95% CI 0.69-0.80; mortality: RR 0.67, 95% CI 0.61-0.75) than in women (incidence: RR 0.86, 95% CI 0.79-0.93; mortality: RR 0.86, 95% CI 0.73-1.01). Neither gFOBT nor sigmoidoscopy screening had any effect on all-cause mortality.

All trials were assigned high risk of bias for selective reporting on harms and burdens, as none of the trials reported how the data was collected. Bleeding requiring hospitalisation and colorectal perforations after screening or subsequent work-up occurred in between 1-3 per 10,000 (0.01 to 0.03 %) individuals screened (low-moderate certainty). Moderate to severe pain was reported by approximately one in five (16-21 % dependent on screening method) individuals undergoing endoscopic procedures (low certainty). Screening

attenders receiving a positive screening test experienced immediate anxiety, but no sustained psychological effects were shown.

This study shows that sigmoidoscopy screening slightly reduces colorectal cancer incidence in a 15-year perspective, while sigmoidoscopy, annual and biennial gFOBT screening all slightly reduce colorectal cancer mortality. Sigmoidoscopy screening may reduce colorectal cancer incidence and mortality more in men than in women. The benefits need to be weighed against possible harms for any individual considering attending screening.

7.2 Paper II

Mortality From Postscreening (Interval) Colorectal Cancers Is Comparable to That From Cancer in Unscreened Patients - A Randomized Sigmoidoscopy Trial.

Gastroenterology 2018;155:1787–1794

We defined interval cancer as any cancer that occurred 30 days or longer after the initial screening, as the flexible sigmoidoscopy screening was intended to be a once-in-a-lifetime event. 163 individuals (1.3%) who underwent screening were later diagnosed with colorectal cancer (interval cancer group); of these, one was diagnosed at surveillance, and 162 were diagnosed due to clinical symptoms. 1740 individuals (2.2%) in the control arm were diagnosed with colorectal cancer (control group); all due to clinical symptoms. The median follow-up was 14.8 years after start of the NORCCAP trial. The median time from study enrolment to cancer diagnosis was slightly longer in the interval cancer group than the control group (10.5 vs 9.9 years, respectively). The distribution of cancer stage was comparable between the two groups (P=0.86).

43 individuals (26.4%) in the interval cancer group died from colorectal cancer, whereas 525 individuals (30.2%) in the control group died from colorectal cancer. The median survival time after colorectal cancer diagnosis was 2.5 years (maximum 13.3 years) in the interval cancer group and 2.8 years (maximum 16.2 years) in the control group. Cox

proportional regression analysis showed that neither colorectal cancer mortality (hazard ratio (HR) 0.98, 95% CI 0.72-1.35, 95% CI -30.1-25.8), rectosigmoid cancer mortality (HR 1.10, 95% CI 0.63-1.92) nor all-cause mortality (HR 0.99, 95% CI 0.76-1.27) differed between the interval cancer group and control group. As colorectal cancer screening is recommended at 10 years intervals in many countries,[24] we performed a sensitivity analysis where follow-up was censored at 10 years, with no significant change in the results.

This study shows that colorectal cancer mortality due to interval cancers is similar to that of cancers in a non-screened population. As colorectal cancers have been estimated to take approximately 10-15 years to develop,[17 21 22] justifying the commonly recommended 10 year-interval between screening episodes, interval cancers comprise the fastest growing cancers. However, we here showed that the rapid growth before causing symptoms did not correlate to worse prognosis.

7.3 Paper III

Long-Term Colorectal Cancer Incidence and Mortality for Women and Men. In submission.

We identified all individuals who had adenomas removed in Norway from 1993 to 2007 through the Cancer Registry of Norway, a total of 40,293 individuals. Previously, we have followed the same cohort through 2011,[69] and now extended the follow-up through 2018. As the exact number of adenomas and the size of adenoma was not registered in the Cancer Registry, we defined high-risk adenomas as ≥ 2 adenomas, adenomas with a villous component or high-grade dysplasia. To validate this modified high-risk classification, we performed a chart review of 948 randomly sampled individuals. The chart review revealed 80% accuracy of the modified criteria, and approximately equal reclassification of both high- and low-risk adenomas among both sexes. The cohort comprised in total 40,293 individuals. Median follow-up was 13.0 years.

1,079 women (5.5%, 440 per 100,000 person-years) and 866 men (4.2%, 364 per 100,000 person-years) developed colorectal cancer during the follow-up. Colorectal cancer incidence was increased both in women and men compared to the general female and male population, respectively, however increased more in women (standardised incidence rate (SIR) 1.64, 95% CI 1.54-1.74) than in men (SIR 1.12, 95% CI 1.05-1.19). In the general population, the absolute risk of colorectal cancer was lower for women (269 per 100,000 person-years) than for men (325 per 100,000 person-years). After adenoma removal, the absolute risk of colorectal cancer was greater for women (441 per 100,000 person-years, 95% CI 414-468) than for men (301 per 100,000 person-years, 95% CI 341-387). Cumulative colorectal cancer incidence was significantly different between individuals with low-risk and high-risk adenomas for both women and men (Gray's test P value<0.001).

328 women (1.7%, 131 per 100,000 person-years) and 275 men (1.3%, 113 per 100,000 person-years) who had an adenoma removed died of colorectal cancer. Colorectal cancer mortality was increased in women who had had an adenoma removed (standardised incidence-based mortality rate (SMR) 1.13, 95% CI 1.02-1.26) compared to the general female population, and decreased in men who had had an adenoma removed (SMR 0.79, 95% CI 0.71-0.89) compared to the general male population. In the general population, the absolute risk of colorectal cancer death was lower for women (116 per 100,000 person-years), than for men (143 per 100,000 person-years). The absolute risk of colorectal cancer death was similar between women and men who had had an adenoma removed (women: 131 per 100,000 person-years, 95% CI 118-146; men: 113 per 100,000 person-years, 95% CI 102-127).

Cumulative colorectal cancer mortality was significantly different between individuals with low-risk and high-risk adenomas for both women and men (Gray's test P value<0.001 for both women and men).

Cox proportional hazard regression analysis, comparing subgroups of individuals who had had adenomas removed to each other, showed that colorectal cancer mortality was

lower among those who had their first adenoma removed in years 2000-2007 (women: HR 0.77, 95% CI 0.61-0.97; men: HR 0.70, 95% CI 0.55-0.90), than those who had their first adenoma removed in 1993-1999. Thus, we performed sensitivity analysis stratified by the period of first adenoma removal, with no significant change in results.

Our study revealed that compared to the general female and male population, women have a significantly higher relative risk of colorectal cancer incidence and mortality after adenoma removal, while men have a higher relative risk of colorectal cancer incidence, but a reduced relative risk of colorectal cancer mortality. Due to the difference in the risk of colorectal cancer death in the background population, women and men who have had adenomas removed have a similar absolute risk of colorectal cancer death.

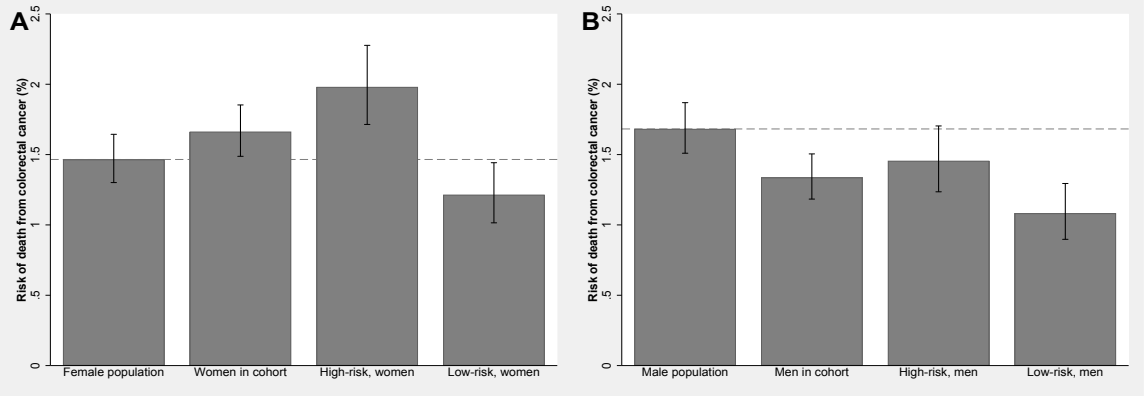

Figure 13: The absolute risk of death from colorectal cancer among (A) women and (B) men who have had an adenoma removed.

8 Discussion of Main Findings

As colorectal cancer screening is offered to more and more people in the world, increasing numbers of individuals have to choose whether to be screened or not. Before implementing population screening and surveillance programmes, the consequences of screening on public health needs to be understood. This is in line with the global campaign "Choosing Wisely", launched by the American Board of Internal Medicine in 2012, and in Norway known as "Gjør kloke valg".[77] This campaign works for patient-centred health care, in which informed decisions on health care is made through conversation with the individual. In all health decisions, one needs to help the individual

choose the care that is evidence-based, not duplicate of care already received, free from harm, and truly necessary. The evaluation of what is perceived as free from harm and truly necessary may differ between individuals, societies and groups, as well as how the evidence-based knowledge is communicated. In addition, the harms and burdens may change with time.

In this thesis, I focus on the effects as well as burdens of colorectal cancer screening and adenoma removal. I present evidence that should be discussed both when considering colorectal cancer screening and surveillance as a public health intervention, and in the conversation with the individual deciding whether or not to participate in screening and surveillance for colorectal cancer.

8.1 Effects of screening and adenoma removal

The effect of colorectal cancer screening on colorectal cancer incidence and mortality with gFOBT and sigmoidoscopy is investigated in several RCTs including several thousands of individuals with long-term follow-up, which were summarised in Paper I: we found that sigmoidoscopy screening reduced the risk of colorectal cancer incidence, and both sigmoidoscopy and gFOBT screening reduced the risk of colorectal cancer mortality. In addition, we found that the effect of colorectal cancer screening with sigmoidoscopy may be less in women than in men. The effect of both sigmoidoscopy and gFOBT screening lasted for at least 15 years.

Today, there are no RCTs with sufficiently long follow-up to evaluate the effect of FIT and colonoscopy screening. Our knowledge about the effect of these two screening methods, that are currently the most used methods, are based on experience from studies on sigmoidoscopy and gFOBT, on the performance on intermediate endpoints (e.g., adenoma detection), and on modelling studies.[78 79] Colonoscopy have higher sensitivity than sigmoidoscopy since the whole colorectum is visualised,[80] and is thus the preferred endoscopic screening method. FIT, on the other hand, may have higher or lower sensitivity and specificity than gFOBT based on the chosen threshold, but is often

preferred due to its specificity to human blood and the practicality of one stool sample only.

Even with high-quality screening, some participants will experience interval cancers. Therefore, individuals attending screening needs to be informed about this and should be encouraged to still react to symptoms of cancer. Paper II shows that interval cancers were diagnosed at the same stage as clinically detected cancers in an unscreened comparison group when the screening attenders were informed about warning symptoms of cancer. In addition, the risk of colorectal cancer mortality was similar for interval cancers compared to other clinically detected cancers.

The effect of adenoma surveillance is dependent on several factors, e.g., the risk classification of the adenomas, the intervals at which surveillance is performed, and the method of surveillance (faecal tests or endoscopic procedures). The traditionally recommended risk classification is mostly based on observational studies of colorectal cancer incidence and mortality after adenoma removal.[31 32] Since this risk classification was established, several new studies have confirmed that colorectal cancer mortality is lower among those who have had low-risk adenomas removed than those who had high-risk adenomas removed.[69 81-85] In addition, some show that those who have had high-risk adenomas removed have higher colorectal cancer mortality than the general population,[69 81 85] or higher risk of colorectal cancer mortality than individuals who are adenoma-free at baseline colonoscopy.[82-84] Paper III confirms the findings of lower risk of colorectal cancer mortality among those who have had low-risk adenomas removed, and higher risk among those who have had high-risk adenomas removed, compared to the general population, even 13.0 years after adenoma removal. In addition, Paper III showed that colorectal cancer mortality is only increased for women and not for men after adenoma removal, compared to the general female and male populations.

In 2020, ESGE published new guidelines for who should be recommended surveillance after adenoma removal, where the risk classification of adenomas was modified due to new evidence:[33 34] Growth pattern was no longer considered an independent risk factor of

colorectal cancer, and the number of adenomas was considered less important. The new high-risk classification of ESGE 2020 included individuals with large adenomas (≥ 10 mm in diameter), or with high-grade dysplasia, or those who had ≥ 5 adenomas removed.[35]

Indeed, our results from Paper III, as well as the previous publication of the same cohort with shorter follow-up,[69] show only a marginal difference in colorectal cancer incidence and mortality between the traditional low-risk and high-risk groups. The groups are also similar of size. This suggests that the traditional risk classification criteria are mostly unable to accurately separate individuals at high-risk from those at low-risk. Ideally, the risk classification system should separate out a small subgroup with true high-risk of later colorectal cancer, and assign the majority to a larger low-risk group in which the risk of cancer is minimal, in order to apply surveillance resources to those in most need.

To investigate the effect of different surveillance policies on the risk of colorectal cancer incidence and mortality, both different intervals and different risk classification systems can be the study target. However, one need to choose whether to study different intervals or classification systems, combining both in one study will make interpretation challenging. The ongoing EPoS trial, investigating the effect of different surveillance intervals after adenoma removal, is based on the traditional risk classification. Results from this trial will not be available before year 2030.[54]

8.2 The individual perspective on screening and surveillance

Shared evidence-based decision-making requires not only studies of effect, but also knowledge about risk communication for the clinician. Risk may be hard for the individual to understand and relate to oneself. However, understanding the risk estimates leads to better informed decision-making. An expert consensus group consisting of fourteen researchers have identified eleven key components of risk communication,[86] which they recommend should be considered when developing tools for risk communication, such as decision aids. The aim of decision aids is to improve the

patient's knowledge of options, the feeling of being well-informed, and clarity of what matters most to them.[87]

Several of the key components of risk communication involves the communication of numeric effects, such as presenting the chance an event will occur.[86] The chance of colorectal cancer in an individual depends on several factors, e.g., sex, age, and life-style. The background risk is essential to be able to apply the relative risk estimates of the studies to the individual, and calculate the individual's absolute risk. Several calculators of individual background risks have been developed,[88] and may be useful in a communicating risk and considering attending screening.

Another key component is to present the change in risk which may occur with the screening.[86] All RCTs on colorectal cancer screening present intention-to-treat analysis. In these analyses, the effect of screening is estimated for everyone randomised to screening, regardless of whether they comply to screening or not. The effect of the screening is given relative to a control group, which has not been offered screening in the trial. However, this control group may have accessed screening outside of the study (i.e., contamination), which may alter the results. The effect estimate of the trial is the average effect expected in a population invited to screening, compared to a population not invited to screening. The intention-to-treat analysis cannot provide the individual effect. For the individual perspective, it may be useful to consider the per-protocol effect, i.e., the effect in the compliers to the screening intervention only. These estimates are, however, only available for some of the RCTs on colorectal cancer screening.[57 58 89] In addition, when considering the per-protocol effect, you compare a selected group of individuals who chose to comply with screening, to a random group of individuals who did not make any choice. The compliers are the more health-concerned individuals,[90] who in addition to attending screening may have other health-inducing behaviours, such as a healthy diet, not being a smoker etc. Thus, the comparison group is no longer valid, and the true individual effect may be overestimated.

In addition to understanding the individual risk of colorectal cancer and the change of risk which may be attributed to screening and subsequent surveillance, the individual also needs to understand the burdens of screening. Some of the burdens of screening are summarised in Paper I: risk of bleeding and perforations are low, between 0.01 and 0.03%, however moderate to severe pain is reported in 16-21% of screened individuals, while the magnitude and significance of the psychological burdens (discomfort of collecting your own stool, distress of travelling to hospital, waiting for the result, and the anxiety associated with an upcoming surveillance) varies greatly. When considering screening, it may be more important to be aware of the possibility of psychological distress, than the frequency at which it occurs: the individual him- or herself probably knows how he or she will be able to cope with this distress.

When considering attending screening, it is important for the individual to be aware of the full picture of the screening process: initially, it is the sieve-sort-intervene process (e.g., FOBT, colonoscopy, adenoma removal), then, it is surveillance if an adenoma is found. No RCT on colorectal cancer screening includes information on burdens after surveillance.

8.3 The public health perspective on screening and surveillance

From the public health perspective, the challenges are slightly different. As Paper I shows, sigmoidoscopy screening reduces colorectal cancer incidence, and both FOBT and sigmoidoscopy screening reduces colorectal cancer mortality. However, neither screening method has an effect on all-cause mortality. Paper III, on the other hand, focus on the challenge of selecting the individuals who will benefit the most for surveillance after adenoma removal, and we find that the long-term colorectal cancer mortality is different between women and men after adenoma removal: it is increased in women who have had adenomas removed, but reduced in men who have had adenomas removed, compared to the general female and male population.

Introducing a screening programme is costly, both monetary and in terms of allocation of resources. In Norway, the cost of a full screening programme with colonoscopy is

estimated to be approximately NOK 250 million (EUR 25 million) per year.[91] This includes the screening test, any necessary work-up, and immediate harms such as bleeding and perforations after colonoscopy. It does not, however, cover the cost and burdens related to adenoma surveillance, such as the necessary increased colonoscopy capacity: individuals will need work-up in relation to the screening test and more individuals will be identified at risk and recommended surveillance. An increased capacity in equipment, rooms and personnel is demanded. Even high-income countries have challenges with the high demand of colonoscopies as a result of screening programmes, and have limited facilities for diagnosis and treatment. The latter is apparent in the Netherlands, where the cut-off of the FIT screening is set higher to accommodate the capacity of colonoscopy facilities.[24]

For screening to be cost-effective for the public, one need to consider whether the lives and life-years gained from colorectal cancer screening justifies this allocation of resources and money. It is important to consider implications of benefits and burdens, and the parts of the population that will benefit the most from both colorectal cancer screening and intervention, as well as the alternative cost. These benefits and burdens may change with time, as knowledge, life-style and technology develops.

8.4 What is low risk?

What is acceptable risk is a value-sensitive question, and individuals and societies will answer differently. Since the relative effect of screening for colorectal cancer seem to be relatively stable in populations with different background risk, the absolute benefit of screening is probably larger in individuals with a higher cancer risk as compared with those with a lower cancer risk. The harms associated with screening, on the other hand, is probably not affected by the individual's cancer risk.

During the development of the BMJ Rapid Recommendations guidelines on colorectal cancer screening,[59] a systematic review of evidence on the magnitude of the reduction in colorectal cancer incidence and mortality required for the individual to undergo screening was performed. The review did not provide clear evidence, and a consensus among the

guideline panel was reached, on the basis of what the panel members believed that the majority of well-informed individuals would choose screening. A weak recommendation in favour of screening, i.e., benefits outweigh the harms for the majority, was thus given if the colorectal cancer risk of the individual exceeded 3% over 15 years.[59]

When introducing a population screening-programme, everyone in a certain age group is invited, e.g., the planned colorectal cancer screening programme in Norway inviting everyone who turns 55 years old. This is independent of the background risk of the individual, but implemented due to the high average background risk of the population. It is not certain that every individual invited will benefit from the screening, however the population on average may benefit. Selecting the individuals with higher risk, either by informing the individuals themselves to make evidence-based decision, or implementing more inclusion criteria to the screening may reduce the burdens of screening without reducing the effect.

Another panel, consisting of gastroenterologists, endoscopists, epidemiologists and experts in public health, similarly tried to reach a consensus on the threshold of colorectal cancer risk for surveillance.[30] The panel reached consensus on that the threshold should be clinically relevant, not only statistically significant, however there was no consensus on the magnitude of a clinically relevant level.

The different comparisons groups used when investigating the risk of colorectal cancer incidence and mortality after adenoma removal illustrates this problem: is the risk of the individuals low enough when it is similar to the general population? Or should the risk level be at a lower level than the general population since the general population comprise a mixture of individuals with and without adenomas? Maybe the right comparison level should be the risk of the adenoma-free? No matter how low we aim, the risk will never reach zero, and an awareness of this among those who are screened and surveilled is important.

The magnitude of what is perceived as low enough risk is dependent on many factors, such as other health challenges of the country, the average background risk of colorectal

cancer, the economy of the country, the perspective from which you look at it (e.g., individual or public), and the capacity of colonoscopy facilities. The lower the risk before intervention, the lower the absolute gain, while the burdens of the intervention remain the mostly unchanged. There is no absolute answer to what a clinically significant low-risk is, and continuous re-evaluation is needed.

8.5 Methodological considerations

8.5.1 Paper I: Network meta-analysis

8.5.1.1 Measure of effect: hazard ratio versus relative risk

Hazard rates are the number of events occurring per survival time, often given as person-years. Thus, the hazard rate considers the length of follow-up, usually given as person-years. Hazard ratios of a screening trial are the ratio of the hazard rates of the screening and control group. The hazard ratio for the study will therefore be the average hazard in one group compared to the other, adjusted for time of follow-up.

Risks, on the other hand, is the probability of an event occurring in a group, i.e., the number of events divided by the number of individuals in the group. The relative risk is also known as the risk ratio: the risk in the exposed (screening) group divided by the risk in the unexposed (control) group. The relative risk may, as hazard ratios, change with time.

The measure of effect in RCTs are most commonly given as hazard ratios or relative risks. In Paper I, we summarise the effect of colorectal cancer screening on colorectal cancer mortality and incidence in a 15-year perspective, as requested by the guideline panel. The number of person-years was not available for all included trials.[58 89] Censoring due to loss of follow-up is unlikely to differ across the randomisation arms, as the included individuals are followed through registries only. We therefore chose to use the relative risk rather than the hazard ratio, using the time point closest to 15 years (range 10.5-19.5 years) of follow-up to facilitate the request by the guideline panel. Sensitivity analyses using person-years as the denominator rather than the number of participants,

and thus excluding the trial in which person-years was not reported, were performed. The results were only slightly different, and would not change the interpretation of the results.

8.5.2 Paper II: A secondary analysis of a randomised controlled trial

8.5.2.1 Definition of interval cancer

It lies within the name "interval cancer" that this is cancers that occur in an interval; to be exact, in the interval between two screening episodes. In this study we have defined any cancer that occurs after a negative screening sigmoidoscopy as an interval cancer, regardless of how much time has passed since the sigmoidoscopy, which is also known as post-screening colorectal cancers. We chose to not set an upper time limit due to the uncertainty of the length of the protective effect of sigmoidoscopy, which in Paper I was shown to be at least 15 years. To account for common practice today, with repeated screening after 10 years,[24] a sensitivity analysis only including interval cancers occurring within 10 years of the screening examination was included. This did not change the results significantly.

8.5.2.2 Comparison groups

Ideally, we would like to compare clinically detected cancers in the screening arm of the randomised NORCCAP trial, to clinically detected cancers in the control arm, in order to have exchangeable groups (Figure 7). However, not all individuals in the screening arm complied with screening. Thus, the clinically occurring cancers in the screening arm was a mixture of clinically detected cancers in non-screened and screened individuals. Among non-compliers in the screening group, a portion of cancers occurring during follow-up would likely have been detected at screening had they attended screening. Including these cancers in the analysis (along with the interval cancers in the compliers), and compare these to the clinically detected cancers in the control arm, would possibly underestimate any difference.

When performing our analysis, we therefore compared interval cancers in the compliers group of the screening arm with clinically detected cancers in the control arm (Figure 7).

The control arm, on the other hand, consists of individuals who, if invited, would both comply and not comply with screening, as they were not informed about the study. Thus, the comparison groups may no longer be exchangeable, and confounding may be introduced.

The individuals complying with screening may be healthier than individuals not complying with screening,[90] and more prone to seek health care when experiencing symptoms. Thus, one may argue that the interval cancers are diagnosed at an earlier stage due to the selection of comparison groups. However, the same individuals may have delayed seeking health care due to the confirmed "healthiness" at screening.[92] Thus, it is not possible to say whether the compliers group seek health care earlier or later than the control group, and the direction of the potential bias is unknown.

In addition to the behavioural effects of those who have been to screening, the interval cancer group differs from the control group in terms of the nature of the detected cancer. Interval cancers comprise three distinct groups (missed lesions, incompletely resected lesions, and newly arisen cancers), while the control group also comprises cancers that would have been prevalent at a screening. Our results show that risk of colorectal cancer death does not differ between interval cancers and other clinically detected cancers. It might be that the risk in the subgroups of interval cancers differ. However, for the clinician considering which treatment is most suitable for the patient, the distinction is not relevant.

8.5.2.3 Stage distribution

With fast-growing lesions and postponed health care seeking after screening as the individual may feel at ease and safe,[92 93] one will expect that interval cancers are diagnosed at later stages of disease than the cancers of the control group. However, our study shows that the staging of disease is similarly distributed between the two groups (P=0.95). To maintain power, we did thus not include stage as a variable in our multivariable model.

8.5.2.4 Subgroups of interval cancers

Since the NORCCAP trial was performed, there has been increasing focus on the quality of endoscopy examinations, including ADR, i.e., the percentage of individuals who have a colorectal adenoma detected at endoscopy, and complete adenoma removals.[94 95] Thus, if this study was repeated today, the proportion of "true" interval cancers (newly arisen cancers) among all cancers detected after screening among the screening compliers would probably be higher. However, for a study performed today, results on colorectal cancer mortality from interval cancers would not be available before in 10-15 years' time. Thus, there is a trade-off between older interventions, long follow-up and clinically relevant end-points versus newer interventions, shorter follow-up and less clinically relevant end-points.

8.5.3 Paper III: Cohort study

8.5.3.1 Causation vs correlation

In cohort studies you do not have two comparison groups that are exchangeable at inclusion, as in RCTs. Thus, in any cohort study, there will be confounders present from the time of inclusion. Some confounders, e.g., sex and age, are well-known, and thus easily adjusted for in the analyses. Other confounders may be unexpected or difficult to measure, and thus not adjusted for. Thus, the differences we observe between the comparison groups may be the results of the confounders that are not adjusted for, rather than the independent variable which we wanted to investigate. Therefore, cohort studies show correlations between the independent and dependent variables unless no residual confounding is assumed. RCTs, on the other hand, may give us causal relationships.

8.5.3.2 Choice of outcome variable

In Paper III, we chose to investigate the long-term outcomes of colorectal cancer incidence and colorectal cancer mortality after adenoma removal. After adenoma removal, individuals are considered to have a clean colon, i.e., no adenomas present. For colorectal cancer to develop according to the adenoma-carcinoma sequence, the

individual then needs to develop an adenoma, which subsequently develops into a cancer. This development is estimated to take on average 10-15 years.[17 21 22] Previous observational studies on the outcomes after adenoma removal have considered several different outcomes which requires different lengths of follow-up: advanced adenomas, colorectal cancer incidence, and colorectal cancer mortality.

Advanced adenomas

Advanced adenoma is used as an intermediate endpoint for the clinically far more important endpoints colorectal cancer incidence and mortality. In comparison to colorectal cancer and death, advanced adenomas take less time to develop, which enable shorter follow-up time of the studies, and the results are available sooner. In addition, advanced adenomas are much more common than colorectal cancer, and smaller study samples are thus required. However, most adenomas do not develop into cancers, and this intermediate endpoint can therefore not be used to estimate the absolute risk of future colorectal cancer, only to look at differences between study groups. Thus, the World Endoscopy Organization considers advanced adenomas an acceptable intermediate endpoint, however at lower validity as the progression time from advanced adenoma to colorectal cancer is not known.[30]

Colorectal cancer incidence

Colorectal cancer incidence is the preferred endpoint to be used in studies after adenoma removal of the World Endoscopy Organization,[30] and the primary aim of adenoma surveillance is to reduce colorectal cancer incidence. However, when considering the correlation between adenoma removal and colorectal cancer incidence, results may be hampered by lead-time bias.

Lead-time is the length of time between early diagnosis of a disease and it's clinical presentation and normal diagnosis.[37] Thus, when any individual is diagnosed with colorectal cancer at screening or surveillance, before symptoms occurs, the length of time between the diagnosis at screening or surveillance and when symptoms would have occurred, is the lead-time. Diagnosis is moved forward. As individuals are diagnosed earlier, the survival time will appear longer because you start the clock earlier.

Guy and Pete

Guy attends colorectal cancer screening, and have a high-risk adenoma removed. He is thus assigned to colonoscopic surveillance in three years. Pete, on the other hand, choose not to attend colorectal cancer screening, and never have an endoscopic examination performed. Pete is thus not included in any surveillance programme. After three years, Guy is diagnosed with colorectal cancer at surveillance, before any symptoms occur. One year later, after end of the observation time, Pete develops a bowel obstruction, and is diagnosed with colorectal cancer. If, however, Pete also had a colonoscopic surveillance the year before, he would have been diagnosed with his colorectal cancer then, before the symptoms occurred, and the observation time ended. The period between the diagnosis of a cancer through screening or surveillance and the time at which the cancer would have been diagnosed due to symptoms, is called lead-time. Due to lead-time in the individual who is surveilled (in this case, Guy), the colorectal cancer incidence is overestimated in the surveilled group compared to the non-surveilled group, i.e., lead-time bias. Thus, if Guy and Pete were to die at the same time, Guy would have contributed with more colorectal cancer survival time than Pete.

Frame 2: Lead-time bias example.

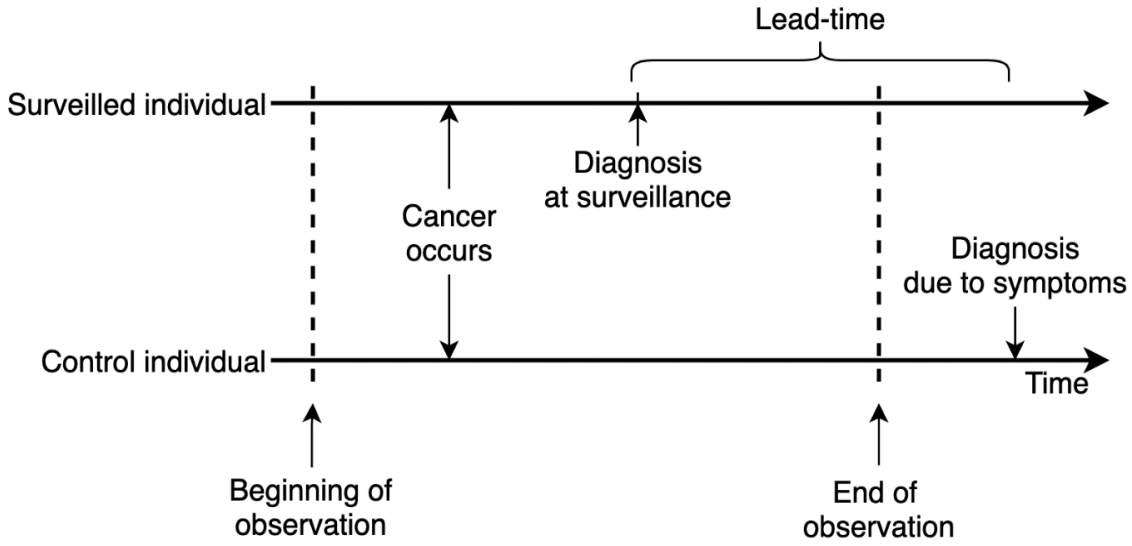

Figure 14: Surveillance and screening may lead to earlier diagnosis of a cancer. When you compare a surveilled individual to a control individual, with no surveillance, the outcome of cancer incidence may be affected by lead-time bias.

Colorectal cancer incidence is also prone to bias due to overdiagnosis, as previously described.

Colorectal cancer mortality

As lead-time and overdiagnosis bias may affect colorectal cancer incidence, World Endoscopy Organization recommends colorectal cancer mortality, the second aim of adenoma surveillance, as a more unbiased outcome.[30] Colorectal cancer mortality requires even longer follow-up time than colorectal cancer incidence. However, mortality cannot be affected by lead-time or overdiagnosis bias. Colorectal cancer mortality may only be affected by prevention and treatment of the cancer.

In Paper III, we chose to report both colorectal cancer incidence and mortality. However, we focus on colorectal cancer mortality as it is the most reliable outcome.

8.5.3.3 Choice of comparison group

In Paper III, we chose to compare our cohort of individuals who had an adenoma removed, to the general population. This is an approach endorsed by the World Endoscopy Organization.[30]

The general population as a comparison group resembles the control group of a screening trial in a screening-naïve population, as it comprises a mixture of individuals with and without adenomas. In any population, you will always have a mixture of individuals who comply or not comply with screening and/or surveillance. Thus, the comparison to the general population gives a real-world estimate of the correlation between adenoma removal and colorectal cancer mortality.

Several previous studies have compared colorectal cancer incidence and mortality of a cohort of individuals after adenoma removal to an adenoma-free population. This comparison group resembles the screening compliers with no adenomas in an RCT. The adenoma-free have an extremely low risk of colorectal cancer.

The aim of colorectal cancer screening and adenoma surveillance is to decrease the risk of colorectal cancer incidence and mortality. The unanswered question is how low the risk should be. Aiming at the risk of the adenoma-free, may warrant intensive surveillance in both women and men after adenoma removal. However, keeping in mind the burdens and costs of screening and surveillance, in addition to the absolute effect, there may be medical areas and interventions that are more cost-effective.

In addition, the comparison of individuals who have had adenomas removed to the adenoma-free introduces the issue of lead-time bias with regards to incidence: the adenoma removal cohort is recommended surveillance, whereas the adenoma-free population is not. In trials, this may be solved by offering everyone a surveillance procedure at the end of follow-up, regardless of previous findings.

8.5.3.4 Generalisability

In contrast to most of the Western world today, the background population in Paper III is mainly screening-naïve. In addition, the individuals of the adenoma cohort were identified due to symptoms.

If the background population was not screening-naïve, the risk of colorectal cancer incidence and mortality in the background population would possibly be lower. However, women and men who have had adenomas removed would also have decreased risk, as many cancers would have been diagnosed at an earlier stage due to screening. The magnitude of the change in risk of colorectal cancer mortality after adenoma removal is hard to estimate, however both cohort and background population would have lower risk. Thus, the change in relative risk due to adenoma removal would probably remain similar. This is also transferrable to other situations, e.g., performing the study in a different country with a lower background risk of colorectal cancer. Both the background population and the women and men who have had adenomas removed would have decreased risk of colorectal cancer, but the change in relative risk due to adenoma removal would probably remain similar.

Biologically, there is no difference in the development of adenomas and colorectal cancers diagnosed by screening and symptomatically. The assumption for most colorectal cancers is still the development through the adenoma-carcinoma sequence. As long as we compare similar to similar, the results can be considered generalizable to other populations.

8.5.3.5 Retrospective studies

During the past decades, more knowledge on the importance of quality of endoscopies, complete removal of adenomas and bowel cleansing has been acquired. Thus, drawing conclusions from retrospective studies where inclusion started decades ago, comes with uncertainties. The clinical practice then might not represent practice today. In addition, in retrospective studies there are no requirements with regards to what to document in the

patient chart, which may cause missing data as well as variables that are not available, e.g., the number of adenomas removed which is not registered in the Cancer Registry in Paper III.

The major benefit of retrospective studies, e.g., cohort studies, is that one may include individuals who had adenomas removed 15 years ago, and compare the outcomes today. In a prospective study, e.g., an RCT, of the outcome after adenoma removal, results will only be available in 10-15 years from the start of the study (inclusion). Then you may have the same issues as in the RCT of Paper II: interventions from the start of the trial may have changed by the time follow-up is stopped. Again, there is a trade-off between change in clinical practice and length of follow-up.

8.6 Ethical considerations

8.6.1 Randomised controlled trials

In RCTs, participating individuals may be randomised before consent (known as Zelen's design or post-randomisation consent)[96] or after consent to participate (known as pre-randomisation consent). In Paper I, one sigmoidoscopy trial and all the gFOBT trials used post-randomisation consent, while the remaining three sigmoidoscopy screening trials used pre-randomisation consent.[58 89 97]

The RCT of Paper II, is the one sigmoidoscopy trial included in Paper I which use post-randomisation consent. Thus, only individuals randomised to the screening arm of the trial, and who chose to participate in the trial, were asked to consent. Those who were randomised to the screening arm, but who chose not to participate in the trial, were not asked for consent. The control arm constituted the remaining individuals of the included age group in the same geographical areas. The individuals of the control arm were not informed of the study nor their participation in it.

Pre-randomisation consent is more commonly used in RCTs. However, when performing an RCT on screening with pre-randomisation consent, individuals complying with screening are more likely to consent to participate in the trial. Thus, you test the effect of

the screening among a selected group of the population; a group which is known to healthier than the rest of the population.[90] The results will reflect the effect of the screening procedure of any individual in the selected group. However, when performing an RCT on screening using post-randomisation consent, as in the NORCCAP trial, you test the effectiveness of a screening programme offered to the whole population when performing intention-to-treat analysis.[98] Even though the first is important for the individual, the latter is a better test of the effect of a population-based screening programme. Thus, the benefit of including individuals without asking for consent to the control arm, is high.

Only information already registered in national health registries (i.e., Cause of Death Registry, Cancer Registry) was used for the individuals who were randomised to the control arm of Paper II, and not informed of the study. Registration in these databases is non-voluntary and compulsory, according to Norwegian legislation. To use already registered information in research, dispensation from patient confidentiality is necessary; either through the consent of the individual, or through evaluation by one of the Regional Ethics Committees of Norway. For the RCT of Paper II, dispensation was given by the Regional Ethics Committee of South-Eastern Norway (2010/3087). The individuals of the control arm received the same health care as if they had not been included in the study. There is, however, a small risk of harm of the individuals in the control arm if the information from the registries is misused, e.g., not properly de-identified before publication. This risk is also present for the compliers to screening, however they have themselves consented to the trial and may such be considered of less harm. In this case, only summarised data and not cases were published, and the risk of identification of individuals is very small. Thus, both we and the ethics committee considered the risk of individuals of the trial smaller than the benefit of knowing the real-world effectiveness of a population-based screening programme for colorectal cancer. The minimal, potential harms of the study groups is justified.

8.6.2 Registry study

The cohort study in Paper III comprises already registered information within the Cancer Registry and Cause of Death Registry of Norway. Only de-identified information was obtained. Thus, as for the RCT above, there is minimal, if any, risk of harm for the individuals included in the study. However, gaining knowledge on the long-term outcomes after adenoma removal, has great benefits; both for the individual who want to receive the appropriate treatment, and for the society who needs to prioritise scarce resources.

8.6.3 Chart review study

The chart review performed as part of Paper III involves the identification of the individuals who had adenomas removed, in order for the researcher to be able to gain access to and study the patient chart. The overall benefit of the study needs to outweigh the harms of the participants. According to Norwegian legislation, all individuals need to consent if others shall have access to their patient chart. However, as the inclusion period of our study was from 1993-2007, approximately one third of the participants were already deceased at the time of chart review.

According to Norwegian legislation, the access to the patient chart of a dead person needs to be evaluated with the interest of the deceased and with the next-of-kin in mind, as well as the interest of the society. Obtaining the consent of all next-of-kin of the deceased included in this study would oppose the data minimisation principle, as we would need detailed information on familial connections, as well as contact details, information otherwise unnecessary to perform the research. We evaluated the risk of the included individual in the study to be small, as there was no intervention, only systematic structuring of already registered health information by dedicated health professionals. At the same time, the benefit of society with increased knowledge on long-term outcomes after adenoma removal was great. Thus, the Regional Ethics Committee of South-Eastern Norway approved that all alive individuals of the chart review study were informed by letter of the study, and they were given the opportunity to reserve themselves from the

study (2014/2352). All deceased individuals, however, were included without any consent or reservation possibility.

9 Conclusion and Implications

9.1 Colorectal cancer screening effect lasts for at least 15 years

Paper I shows that sigmoidoscopy screening slightly reduces colorectal cancer incidence in a 15-year perspective after a once-only screening. Screening with sigmoidoscopy and repeated gFOBT, performed annually or biennially, slightly reduce colorectal cancer mortality in the same 15-year perspective. Most guidelines today recommend rescreening after 10 years; however, our finding suggest that the protective effect may be even longer-lasting, and thus longer screening intervals can be considered. As resource expenditure, and most harms of colorectal cancer screening happen in relation to the screening test itself, this may also lessen the burden of the screening programme and screening attenders.

Future studies should consider the effect of colorectal cancer screening with longer intervals, and using colonoscopy and FIT as screening methods. A once-in-a-lifetime screening at an appropriate age may be sufficient to recognise individuals at increased risk of colorectal cancer.

9.2 Interval cancers have similar prognosis as other clinically detected cancers

Increasing the interval at which screening occurs, may cause more interval cancers. However, Paper II shows similar colorectal cancer stage distribution and mortality when comparing individuals diagnosed after a screening episode (i.e., interval cancers) to individuals who have never been offered screening. Even though the true interval cancers may be more fast-growing for a period, they do not necessarily continue their aggressive growth. Therefore, the clinician should not consider screening history when choosing treatment for the patient, but follow normal clinical guidelines. This finding is in line with findings on interval cancers from mammography,[99] PSA[100] and gFOBT[101] screening.

All participants of cancer screening programmes should be well informed about the risk of interval cancer. It is of outmost importance that the individual does not change behaviour after screening, and a negative screening examination should not be considered a certificate of health.[92]

Interval cancers should be continuously studied as clinical practice evolves, e.g., increased focus on ADR and complete removal of adenomas today compared to our study period, may have changed the proportion of "true" interval cancers. However, as it takes >10 years to achieve results, results continuously needs to be re-evaluated.

9.3 Sex-specific screening and surveillance guidelines should be implemented

When interpreting the results of Paper III, it is important to consider whether the cohort was surveilled during follow-up or not.[30] Until year 2013, i.e., most of the study period, there was little surveillance in Norway, where only individuals <75 years of age were offered surveillance: after 10 years if they had advanced adenomas (defined as high-grade dysplasia, villous growth pattern, or diameter ≥ 10 mm), or after 5 years if they had ≥ 3 adenomas removed.[68] Thus, members of this cohort had much less intensive surveillance than what is recommended today and is more similar to individuals in a health-care system where screening is recommended at 10-year intervals.

When comparing women in our cohort of individuals who have had adenomas removed (Paper III) to the general female population, we find that women have a slightly increased risk of colorectal cancer mortality after adenoma removal. When comparing men who have had adenomas removed in our cohort to the general male population, we find that men have a reduced risk of colorectal cancer mortality after adenoma removal. However, the absolute risk level is quite similar for both women and men after adenoma removal, while the background risk of colorectal cancer mortality is lower among the female than male general population. Thus, the observed excess risk for women after adenoma removal and the reduced risk for men after adenoma removal may not be due to different effect of adenoma removal between women and men, but rather the difference in background colorectal cancer mortality risk.

The apparent smaller reduction in colorectal cancer mortality in women, however, may also be due to a different pathogenesis of colorectal cancers in women, where adenoma removal has less effect on colorectal cancer mortality, e.g., because other cancer pathways than the adenoma-carcinoma pathway dominates. Together with the results of Paper I, which showed that sigmoidoscopy screening has less effect in women than in men, one may question whether sex-specific guidelines for screening and surveillance are warranted.

Further, when shaping surveillance policy, which include to decide whether or not to implement sex-specific surveillance guidelines, one need to consider what we want to achieve with surveillance, what is acceptable risk, and what we mean by equality in health services. Since women have increased colorectal cancer mortality after adenoma removal compared to their general population peers, one may argue that women should have more intensive surveillance after adenoma removal. Men, on the other hand, with reduced colorectal cancer mortality after adenoma removal, are not in need of intensive surveillance as their risk is lower than the general population. However, if one aim at a lower acceptable risk threshold than the general population, e.g., the risk of the adenoma-free, one may argue that intensive surveillance is warranted in both sexes.

Future studies should focus on why there is a difference in women and men; does colorectal cancer in women have a different pathogenesis than in men? In particular, the importance of serrated polyps, which were not included in our cohort, nor the focus of the screening trials, should be studied. In addition, if the difference in risk of colorectal cancer incidence and mortality between the sexes is similar both for FIT and colonoscopy screening, should be an area of future research.

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11 Papers

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BMJ Open

Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis

Henriette C Jodal ,[1,2,3] Lise M Helsingen ,[1,2,3] Joseph C Anderson,[4,5,6] Lyubov Lytvyn,[7] Per Olav Vandvik,[8,9] Louise Emilsson[1,10,11]

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For numbered affiliations see end of article.

Correspondence to
Dr Henriette C Jodal;
h.c.jodal@medisin.uio.no

ABSTRACT

Objective Evaluate effectiveness, harms and burdens of faecal blood testing, sigmoidoscopy and colonoscopy screening for colorectal cancer over 15 years.

Design We performed an update of a Cochrane systematic review, and performed network meta-analysis comparing randomised trials evaluating colorectal cancer screening with guaiac faecal occult blood test (gFOBT) (annual, biennial), faecal immunochemical test (FIT) (annual, biennial), sigmoidoscopy (once-only) or colonoscopy (once-only) in a healthy population, aged 50–79 years. We conducted subgroup analysis on sex. Follow-up >5 years was required for analysis of colorectal cancer incidence and mortality.

Results 12 randomised trials proved eligible. Compared with no-screening, we found high certainty evidence for sigmoidoscopy screening slightly reducing colorectal cancer incidence (relative risk (RR) 0.76; 95% confidence interval (CI 0.70 to 0.83) and mortality (RR 0.74; 95% CI 0.69 to 0.80), while gFOBT screening had little or no difference on colorectal cancer incidence, but slightly reduced colorectal cancer mortality (annual: RR 0.69; 95% CI 0.56 to 0.86, biennial: RR 0.88; 95% CI 0.82 to 0.93). No screening test reduced mortality nor incidence by more than six per 1000 screened over 15 years. Sigmoidoscopy had a greater effect in men, for both colorectal cancer incidence (women: RR 0.86; 95% CI 0.81 to 0.92, men: RR 0.75, 95% CI 0.71 to 0.79), and mortality (women: RR 0.85; 95% CI 0.71 to 0.96, men: RR 0.67; 95% CI 0.61 to 0.75) (moderate certainty).

Conclusions In a 15-year perspective, sigmoidoscopy reduces colorectal cancer incidence, while sigmoidoscopy, annual and biennial gFOBT all reduce colorectal cancer mortality. Sigmoidoscopy may reduce colorectal cancer incidence and mortality more in men than in women.

PROSPERO registration number CRD42018093401.

Strengths and limitations of this study

- ► This is the first review on colorectal cancer screening including estimates from three of the major sigmoidoscopy screening trials after as long as 14.8 years of follow-up.
- ► This is the first meta-analysis to assess the subgroup effect of sigmoidoscopy screening by sex from all four major sigmoidoscopy trials.
- ► This review was conducted based on a a priori protocol, and designed by input from professionals and patient partners in a BMJ Rapid Recommendations guideline panel.
- ► This review provides absolute risks in addition to relative estimates in a 15-year perspective after initial screening episode.
- ► We only look at effects of screening in randomised controlled trials.

INTRODUCTION

Colorectal cancer is a major global health burden. It is the third most common cancer worldwide, and the second most cause of cancer-related deaths.[1] Colorectal cancers may arise from precancerous lesions known as adenomas.[2] Both adenomas and colorectal cancers can be visualised during sigmoidoscopy and colonoscopy. Even before symptoms occur, colorectal cancers might cause occult bleeding, which can be discovered by faecal blood tests known as guaiac faecal occult blood test (gFOBT) and the more recently developed faecal immunochemical test (FIT). gFOBT, FIT, sigmoidoscopy and colonoscopy are all used as screening methods for colorectal cancer.

Cancer screening are based on two different principles: early detection and prevention.[3] Early detection of cancer enables treatment of cancer before it reaches an incurable state, and may thus reduce cancer mortality. Preventive cancer screening, on the other hand, is to detect and remove precursor lesions to cancers, such as colorectal adenomas. Thus, preventive screening may cause a reduction in both cancer incidence and subsequently mortality.[3]

Prior systematic reviews and meta-analyses evaluating the effectiveness of colorectal cancer screening showed that sigmoidoscopy screening reduces colorectal cancer

Box 1 Linked articles in this BMJ Rapid Recommendation cluster

- Helsingen *et al*. Colorectal cancer screening with faecal immunochemical test, sigmoidoscopy or colonoscopy: a clinical practice guideline.[16]
  Summary of the results from the Rapid Recommendation process.
- Jodal *et al*. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis.
  Systematic review and network meta-analysis of all available trials that assessed colorectal cancer screening.
- Buskermolen *et al*. Colorectal cancer screening with faecal immunochemical test, sigmoidoscopy or colonoscopy: a microsimulation modelling study.[56]
  Modelled estimates of benefits and harms of screening after 15 years for different levels of baseline risk of colorectal cancer.
- MAGICApp (http://magicproject.org/190220dist).
  Expanded version of results with multilayered recommendations, evidence summaries and decision aids for use on all devices.

incidence, while both sigmoidoscopy and gFOBT reduce colorectal cancer mortality.[4–7] Recently, updates of three major trials on once-only sigmoidoscopy screening have been published: the UK Flexible Sigmoidoscopy Screening (UKFSST),[8] the Norwegian Colorectal Cancer Prevention (NORCCAP)[9] and the Prostate, Lung, Colorectal and Ovarian cancer (PLCO)[10] trials. These updates provide estimates on reduced colorectal cancer incidence and mortality after a median follow-up of approximately 15 years or longer. In addition, these updates suggest a subgroup effect of screening on sex, with men experiencing greater reduction in both incidence and mortality than women.[8–11]

This is the first systematic review and meta-analysis including these updated results, and thus provides estimates for the risk of colorectal cancer incidence and mortality as long as 15 years after screening initiation. This review informed a clinical practice guideline, developed in parallel as a part of the BMJ Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation programme (www.magicproject.org) and *The BMJ*. The aim of the project is to respond to new potentially practice changing evidence and provide a trustworthy practice guideline in a timely manner.[12] Box 1 shows the articles linked to this BMJ Rapid Recommendation cluster.

METHODS

Protocol and registration

The protocol for this systematic review was registered with PROSPERO (CRD42018093401).[13]

BMJ Rapid Recommendations and patient involvement

According to the BMJ Rapid Recommendations process,[12] a guideline panel provided critical oversight to the review. The panel identified populations, screening methods, subgroups and patient-important outcomes of interest a priori, based on most common screening practice today.[14 15] The panel requested evidence in a 15-year perspective, as the recent publications that prompted the recommendations evaluated once-only sigmoidoscopy screening after approximately 15 years of follow-up. The panel included patient partners (individuals with experience of colorectal cancer screening), general practitioners, general internists, gastroenterologists, content experts in colorectal cancer screening, methodologists and a nurse practitioner. The patient partners were full members of the guideline panel, and contributed to the selection and prioritisation of outcomes together with the rest of the panel, under guidance of a patient liason. The panel members helped interpret the evidence in this review and make clinical practice recommendations.[16]

Search strategy

We updated a previously published Cochrane systematic review search.[4] The search previously ended in November 2012, while we updated the search until 17 December 2018. A trained medical librarian searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials for published randomised controlled trials, with no language restrictions (online supplementary appendix 1). We reviewed reference lists from eligible new trials and related reviews for additional citations.

Study selection

We imported all citations into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Two reviewers (HCJ and LMH) independently screened titles, abstracts and full texts according to the eligibility criteria. Since this is an update of a previously published systematic review,[4] we also screened the full texts of all the studies that were included and excluded at the full-text screening stage by the authors of the original review.

We considered all randomised controlled trials in any language comparing annual or biennial gFOBT or FIT, once-only sigmoidoscopy or once-only colonoscopy, compared with no-screening or to one another, in a healthy population aged 50–79 years, as requested by the panel.[16] Outcomes of interest were colorectal cancer incidence and mortality, all-cause mortality, harms (bleeding, perforation, screening-related death and other major and minor complications as reported by trial authors) and burdens (need for further diagnostic workup including colonoscopy, procedure-related pain, psychological impact of a positive test and absence from work to prepare, perform and recover after the screening procedure).

Meta-analyses have shown that it takes at least 5 years from screening until an effect on colorectal cancer mortality or incidence can be observed.[17 18] Thus, for analyses of colorectal cancer incidence and mortality, as well as all-cause mortality, we only included trials where follow-up was at least 5 years. Harms and burdens, on the

other hand, are experienced during or soon after the screening procedure, and thus no follow-up restrictions were applied to the analyses of these outcomes.

Data extraction and rating of evidence

Two reviewers (HCJ and JCA) independently extracted data using a standardised form. From each eligible trial we collected the following information: study characteristics (study design, description of intervention, study period), description of participants (number, screening adherence, age and sex distribution), length of follow-up and outcomes data (events and numbers of patients included for analyses in each group). Reviewers had a third party available to resolve disagreement, however it was not needed. The authors of studies that did not report all outcomes of interest (eg, sex subgroups) were contacted.

Two reviewers (HCJ and LMH) independently assessed risk of bias using a modified version of the Cochrane tool,[19] assessing the domains random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance and detection bias), incomplete outcome data (attribution bias), selective reporting (reporting bias) and other bias. For each domain, the risk of bias was judged as low or high. Reviewers had a third party available to resolve disagreement, however it was not needed. We followed the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to rate the certainty of evidence of estimates derived from pairwise and network meta-analysis.[20] We rated direct, indirect and network meta-analysis (NMA) estimates separately. We used the lower certainty rating of the two pairwise estimates contributing as first-order loop for indirect comparisons.[21 22] To rate the NMA estimates, we evaluated the ratings of the direct and indirect evidence and their coherence.[21 22] Harms and burdens from screening will only occur in individuals attending screening, and is thus prognostic. Therefore, we evaluated the certainty of the evidence on harms and burdens using GRADE for assessment of evidence about prognosis.[23]

Data synthesis and analysis

Intention-to-treat numbers were used for all analyses regarding incidence and mortality. In one of the trials,[9] the ratio of screened to control participant differed in different age groups (1:3 vs 1:5.4), thus the average age in the screened and the control groups differed. Therefore, these two age groups are analysed as two separate trials in this NMA. We performed standard pairwise comparisons of each screening intervention versus no-screening, using a restricted maximum likelihood approach to estimate relative risks (RR) with 95% CIs. Between-study variances were made equal, and correlations were set to 0.5. We examined statistical heterogeneity among studies using the Cochran Q-test (significant if $p<0.10$) and the between-study variance tau.[2] Furthermore, an NMA applying mixed-treatment models based on a random-effects model in a frequentist framework was performed to compare the different interventions, using the mvmeta program and network graphs package for Stata.[24] We report RRs for direct, indirect and network estimates and associated 95% CIs. We used the node-splitting approach for the assessment of loop inconsistency. We used the mean risk of events in the comparison groups to calculate the absolute effects of treatment in a 15-year perspective. We performed a sensitivity analysis including the 30-year follow-up of one of the gFOBT trials,[25] and another sensitivity analysis excluding the PLCO trial,[10] as this trial included a second sigmoidoscopy screening episode 3 or 5 years after the initial screening. As the length of follow-up varies between the studies, we also performed sensitivity analyses using person-years as the denominator rather than number of participants, and we report HRs for network estimates.

Subgroup differences in incidence and mortality between women and men were analysed using a fixed-effect meta-analysis. To further explore the effect modification for sex, we used a one-stage multilevel meta-regression model including screening intervention, sex and interaction term between sex and intervention as fixed-effect covariates, and study as a random-effect covariate. Furthermore, we fit a meta-analysis using only within-study comparisons, that is, pooling the risk differences (the deft approach).[26] We excluded studies that did not report outcomes separately for men and women.

Harms and burdens as selected by the guideline panel were analysed using meta-analyses for binomial data using the metaprop_one Stata package modelling random effects and exact CIs. Analysis of psychiatric harms was not possible due to differences in reporting, and is therefore only descriptive. All numbers on harms and burdens are presented as proportions of patients who underwent screening, that is, per-protocol numbers.

We used Stata V.15.1 for all data analyses (StataCorp, College Station, Texas, USA). We followed the reporting standards set by Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[27] and the PRISMA-NMA extension statement[28] for all aspects of the review (online supplementary appendix 2).

RESULTS

Description of included studies

Our search yielded 8992 potentially relevant records. Combined with the result from the previously published review,[4] a review of reference lists and updates of included trials published after our search was performed, a total of 12 different randomised trials described in 36 articles were included in this review (figure 1, table 1). Five trials included gFOBT screening, two included FIT screening, five included sigmoidoscopy screening and two included colonoscopy screening.

The included trials enrolled a total of 1 325 618 participants, from Denmark, Italy, the Netherlands, Norway,

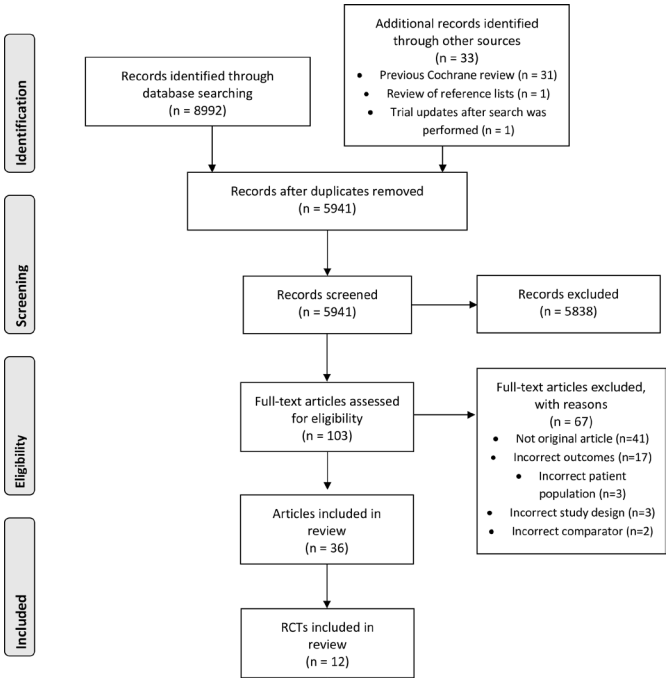

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram of study selection for systematic review and meta-analysis.[27] RCT, randomised controlled trial.

Poland, Spain, Sweden, the UK and the USA, with follow-up ranging from 0 to 19.5 years for colorectal cancer incidence, and 0 to 30 years for colorectal cancer mortality. The age of invited participants ranged from 45 to 80 years, with an equal distribution of men and women. The gFOBT trials have reported results from 1 to 11 screening rounds, while the FIT trials, both still ongoing, have reported results from none to one screening round. One of the gFOBT trials performed annual screening, while five performed biennial screening.

The studies included in this review deviate slightly from the panel's request for evidence on a healthy population aged 50–79 years, as two of the gFOBT trials included individuals from 45 years of age.[29 30] In addition, one of the sigmoidoscopy trials included some participants who were screened twice,[10] in contrast to the panel's request for evidence on once-only sigmoidoscopy screening.

The trials varied in follow-up time after screening intervention, from 0 to 30 years. However, for the trials exceeding >5 years of follow-up, which were thus included in the analyses of incidence and mortality, the follow-up ranged from 10.5 to 30 years. One of the included trials[25] had a maximum follow-up time substantially longer than the others (30 years vs 10.5–19.5 years), and we therefore chose to extract data from the 18-year follow-up of this trial.[31] Thus, all trials had approximately 15 years of follow-up (range 10.5–19.5 years) for the analyses of incidence and mortality, which was also relevant to the guideline panel's goal of providing 15 years estimates for different screening interventions.[16]

All trials had at least one criterion at high risk of bias. For the outcomes of incidence and mortality, only one report was assigned high risk of bias for incomplete data, due to a high withdrawal of consent from the participants.[32] None of the trials were assigned high risk of bias for selective reporting of the outcomes incidence and mortality, but several were so for harms and burdens (figure 2, online supplementary appendix 3).

Effects on incidence and mortality

Eight of the randomised trials had >5 years of follow-up, and were thus included in the analyses of incidence and mortality: four studies on gFOBT screening, and four on sigmoidoscopy screening (figure 3).

Sigmoidoscopy screening slightly reduced colorectal cancer incidence (RR 0.76; 95% CI 0.70 to 0.83) (figure 4) and colorectal cancer mortality (RR 0.74; 95% CI 0.69 to 0.80) (figure 5) compared with no-screening. In a 15-year perspective, this corresponds to a reduction of six (eight to four fewer) colorectal cancer cases per 1000 individuals screened, and a reduction of three (three to two fewer) colorectal cancer deaths per 1000 individuals screened. The certainty of evidence was high (table 2).

gFOBT screening made little or no difference on colorectal cancer incidence compared with no-screening, neither annually nor biennially (annual: RR 0.86; 95% CI 0.72 to 1.03, biennial: RR 0.95; 95% CI 0.87 to 1.04) (figure 4). Colorectal cancer mortality was slightly reduced for both annual and biennial gFOBT screening compared with no-screening (annual: RR 0.69; 95% CI 0.56 to 0.86, biennial: RR 0.88; 95% CI 0.82 to 0.93) (figure 5). In a 15-year perspective, this corresponds to a reduction of one (three fewer to one more) colorectal cancer case and one (two to one fewer) colorectal cancer death per 1000 screened individuals when screened biennially, and a reduction of four (seven fewer to one more) colorectal cancer cases and three (four to one fewer) colorectal cancer deaths per 1000 screened individuals when screened annually. The certainty of evidence for comparisons involving biennial gFOBT screening was high (table 2). The certainty of evidence was downgraded for all comparisons involving annual gFOBT screening due to serious imprecision, as this evidence is based on estimates from only one trial and the rate of events is low (table 2). Direct and indirect estimates are available in online supplementary table 1A.

Sigmoidoscopy screening slightly reduced colorectal cancer incidence (RR 0.80; 95% CI 0.71 to 0.91) (figure 4) and mortality (RR 0.85; 95% CI 0.77 to 0.93) (figure 5) compared with biennial gFOBT. In a 15-year perspective, this corresponds to an absolute reduction of six (eight fewer to three fewer) colorectal cancer cases and a reduction of two (three to one fewer) colorectal cancer deaths per 1000 individuals screened. The certainty of evidence was high (table 2).

Sigmoidoscopy compared with annual gFOBT screening probably had little or no difference on colorectal cancer incidence (RR 0.89; 95% CI 0.73 to 1.09) (figure 4) and mortality (RR 1.07; 95% CI 0.85 to 1.34) (figure 5),

Table 1 Characteristics of studies included in the systematic review

Study	Country	Design	Screening modality	Study period	Age	Standard care (n)	Screening group (n)	Men/women (n)	Adherence (%)	Follow-up (years)
Atkin [8 41 46 57]	UK (UKFSST)	Volunteers	Sigmoidoscopy, once only	1994–1999	55–64	113 178	57 254	83 334 / 86 700	71	Median 17.1
Schoen [11 32 42 58 59]	US (PLCO)	Volunteers	Sigmoidoscopy, twice	1993–2001	55–74	77 444	77 443	76 678 / 78 209	83.5	Mortality median 16.8; Incidence median 15.8
Segnan [11 43 60]	Italy (SCORE)	Volunteers	Sigmoidoscopy, once only	1995–1999	55–64	17 144	17 148	17 235 / 17 158	57.8	Mortality median 11.4; Incidence median 10.5
Hoff [9 11 44 61–63]	Norway (NORCCAP)	Population-based	Sigmoidoscopy, once only	1999–2001	50–64	79 430	20 780	49 191 / 49 601	65	Median 14.8
Mandel [25 31 38 64]	USA (Minnesota)	Volunteers	gFOBT, annually* and biennially†	1975–1992	50–80	15 394	Annual: 15 570; Biennial: 15 587	Annual: 7489/8081; Biennial: 7444/8143	Annual: 90.2; Biennial: 89.9	Mortality: 30; Incidence: 18
Scholefield [29 34 35 48 65]	England (Nottingham)	Population-based	gFOBT, biennially‡	1981–1995	45–74	76 384	76 253	72 172 / 78 079	59.6	Median 19.5
Kronborg [30 36 66]	Denmark (Funen)	Population-based	gFOBT, biennially§	1985–2002	45–75	30 966	30 967	29 714 / 32 219	66.7	Max 17
Kewenter [37 49 67 68]	Sweden (Gothenburg)	Population-based	gFOBT, biennially¶	1982–1995	60–64	34 164	34 144	NR	70	Mean 15.5
Pitkaniemi [39]	Finland	Population-based	gFOBT, biennially**	2004–2012	60–69	181 085	181 080	179 519 / 180 973	68.8	Median 4.5
Quintero [69]	Spain (COLONPREV)	Population-based	Colonoscopy, once only/ FIT (15 µg/g), biennially**	2008–2011	50–69	NA	Colonoscopy: 28 708; FIT: 28 696	26 463 / 30 941	Colonoscopy: 24.6; FIT: 34.2	0
Bretthauer [70]	Norway, Sweden, Poland, the Netherlands (NORDICC)	Population-based	Colonoscopy, once only	2009–2014	55–64	63 370	31 589	47 259 / 47 135	40.0	0
Kirkøen [47]	Norway (BCSN)	Population-based	Sigmoidoscopy, once only/ FIT (15 µg/g), biennially**	2001–2008	50–74	7650	Sigmoidoscopy: 7270; FIT: 6920	10 088 / 11 752	Sigmoidoscopy: 51; FIT: 57	0

Continued

Table 1 Continued

Study	Country	Design	Screening modality	Study period	Age	Standard care (n)	Screening group (n)	Men/women (n)	Adherence (%)	Follow-up (years)

*Eleven screening rounds over 15 years, with a 4-year hiatus.
†Six screening rounds over 15 years, with a 3-year hiatus.
‡Three to five screening rounds.
§Nine screening rounds.
¶Two to three screening rounds, interval between rounds maximum 10 years 2 months.
**Ongoing.
BCSN, Bowel Cancer Screening in Norway; COLONPREV, Colorectal Cancer Screening in Average-risk Population; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; NORCCAP, Norwegian Colorectal Cancer Prevention trial; NORDICC, The Northern-European Initiative on Colorectal Cancer; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; SCORE, Italian multicentre randomised controlled trial of once-only sigmoidoscopy; UKFSST, UK Flexible Sigmoidoscopy Screening Trial.

Figure 2 Risk of bias summary for each clinical trial included in the systematic review.

corresponding to an absolute reduction of three (seven fewer to two more) colorectal cancer cases, and an increase of one (one fewer to three more) colorectal cancer death per 1000 individuals screened in a 15-year perspective. The certainty of evidence was downgraded due to serious imprecision, as the evidence of the effect of annual gFOBT

Figure 3 Network of included trials with available direct and indirect comparisons. The number next to each line is the number of studies comparing the connecting interventions. gFOBT, guaiac faecal occult blood test.

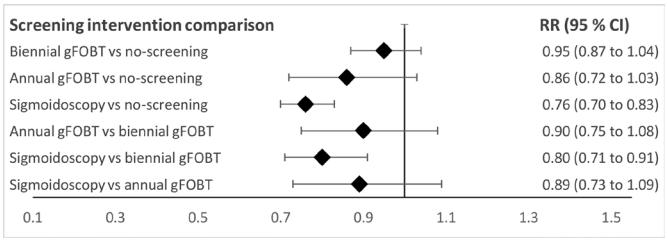

Figure 4 Effect of different screening interventions on colorectal cancer incidence shown as relative risks (RR) with 95% CIs. gFOBT, guaiac faecal occult blood testing.

screening is based on estimates from only one trial and the rate of events is low (table 2).

Annual compared with biennial gFOBT screening probably has little or no difference on colorectal cancer incidence (RR 0.90; 95% CI 0.75 to 1.08) (figure 4), but probably reduced colorectal cancer mortality slightly (RR 0.79; 95% CI 0.64 to 0.98) (figure 5). In a 15-year perspective, this corresponds to an absolute reduction of three (seven fewer to two more) colorectal cancer cases, and three (four fewer to zero) colorectal cancer deaths per 1000 individuals screened. The certainty of evidence was downgraded due to serious imprecision, as the evidence of the effect of annual gFOBT screening is based on estimates from only one trial and the rate of events is low (table 2). Direct and indirect estimates are available in online supplementary table 1B.

All-cause mortality showed little or no difference among any of the screening interventions (online supplementary figure 1). For direct and indirect estimates, see online supplementary table 1A-B. The heterogeneity of the only loop in the network (annual gFOBT—biennial gFOBT—no-screening) could not be estimated due to insufficient observations, and reports of inconsistency are therefore abundant.

Sensitivity analyses including the 30-year follow-up of one of the gFOBT trials[25] had no significant impact on the results. Sensitivity analysis excluding the PLCO trial[10] on sigmoidoscopy screening (participants screened with sigmoidoscopy twice) had no significant impact of the results. A post hoc sensitivity analysis excluding the UKFSST trial[8] on sigmoidoscopy was also performed, as this trial contributed to statistical heterogeneity in colorectal cancer incidence. This had no significant impact of the effect estimates, however moved the point estimates slightly towards the null. Therefore, this statistical heterogeneity was not considered a serious concern. Sensitivity analyses calculating hazard ratios (HR rather than RR, showed only minor differences, none of which affect the interpretation of the results (online supplementary figures 2-4).

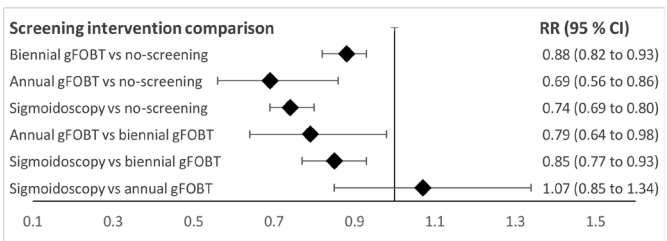

Figure 5 Effect of different screening interventions on colorectal cancer mortality shown as relative risks (RR) with 95% CIs. FOBT, faecal occult blood testing.

Sex differences

The subgroup analyses suggested a sex difference for sigmoidoscopy screening (table 3). Pairwise fixed-effect meta-analyses showed heterogeneity between the sexes for both colorectal cancer incidence (women: RR 0.86; 95% CI 0.81 to 0.92, men: RR 0.75; 95% CI 0.71 to 0.79, p=0.001) (figure 6) and mortality (women: RR 0.85; 95% CI 0.71 to 0.96, men: RR 0.67; 95% CI 0.61 to 0.75, p=0.006) (figure 7), but not for all-cause mortality (online supplementary figure 5). The one-stage multilevel model for sex and effect of sigmoidoscopy was statistically significant for interaction (incidence: p=0.001, mortality: p=0.015). Using the deft approach, we obtained similar results (colorectal cancer incidence risk difference 11% (95% CI 3% to 20%); colorectal cancer mortality risk difference 17% (95% CI 1% to 34%)). We assessed the credibility of these observed subgroup differences to be moderate (online supplementary table 2),[33] supporting a greater relative effect of sigmoidoscopy in men than in women, for reducing colorectal cancer incidence and mortality.

Harms and burdens

The gFOBT trials reported harms in different ways: three of the trials[34–37] reported harms summarised after several screening rounds where only those who had attended the previous screening episode were re-invited, while the two other trials[38 39] reported harms and total number of screening tests where all randomised participants were re-invited even though they chose not to attend the first or previous screening episodes. We therefore pooled the harms and burdens events from gFOBT screening trials data in two groups: 1) reported as a total from two to five screening rounds and 2) reported per performed screening test, assuming that harms and burdens were independent of the screening round. The sigmoidoscopy trials reported harms and burdens from the screening procedure including subsequent workup. Due to the differences in reporting, we were not able to pool estimates across screening interventions. All trials reported the total number of events. None of the trials, regardless of screening intervention, have reported harms and burdens following surveillance procedures.

Perforation and bleeding requiring hospitalisation

Eight out of the total of 11 trials reported on bleeding requiring hospitalisation and nine reported on perforations after screening, either from the screening procedure itself or subsequent workup. The risk of bleeding in the sigmoidoscopy trials was 3 (1–6) per 10 000 (0.03%; 95% CI 0.01% to 0.06%) screening attenders, while for colonoscopy it was 17 (12–23) per 10 000 (0.17%; 95% CI 0.12% to 0.23%) (figure 8). The risk of bleeding in the gFOBT trials were none (zero to one) per 10 000 (0.00%; 95% CI 0.00% to

Table 2 Relative and absolute NMA effect estimates for incidence and mortality in a 15-year perspective comparing the different screening interventions and no-screening

Outcome	Study results and measurements	Absolute effect estimates			Certainty in effect estimates	Plain text summary
		Comparator	Intervention	Difference (95% CI)		
No-screening vs sigmoidoscopy screening						
Colorectal cancer incidence	RR 0.76 (95% CI 0.70 to 0.83) based on data from 614 397 patients in eight studies. Follow-up 10.5–19.5 years.	26 per 1000	20 per 1000	6 fewer per 1000 (8 fewer to 4 fewer)	High	Sigmoidoscopy slightly reduces colorectal cancer incidence.
Colorectal cancer mortality	RR 0.74 (95% CI 0.69 to 0.80) based on data from 614 428 patients in eight studies. Follow-up 11.4–17.1 years.	10 per 1000	7 per 1000	3 fewer per 1000 (3 fewer to 2 fewer)	High	Sigmoidoscopy slightly reduces colorectal cancer mortality.
All-cause mortality	RR 0.99 (95% CI 0.98 to 1.00) based on data from 614 431 patients in eight studies. Follow-up 11.4–19.5 years.	269 per 1000	266 per 1000	3 fewer per 1000 (5 fewer to 0)	High	Sigmoidoscopy has little or no difference on all-cause mortality.
No-screening vs biennial gFOBT screening						
Colorectal cancer incidence	RR 0.95 (95% CI 0.87 to 1.04) based on data from 598 865 patients in eight studies. Follow-up 10.5–19.5 years.	26 per 1000	25 per 1000	1 fewer per 1000 (3 fewer to 1 more)	High	Biennial gFOBT screening has little or no difference on colorectal cancer incidence.
Colorectal cancer mortality	RR 0.88 (95% CI 0.82 to 0.93) based on data from 598 933 patients in eight studies. Follow-up 11.4–19.5 years.	10 per 1000	9 per 1000	1 fewer per 1000 (2 fewer to 1 fewer)	High	Biennial gFOBT screening slightly reduces colorectal cancer mortality.
All-cause mortality	RR 1.00 (95% CI 0.99 to 1.01) based on data from 598 934 patients in eight studies. Follow-up 11.4–19.5 years.	269 per 1000	269 per 1000	0 fewer per 1000 (3 fewer to 3 more)	High	Biennial gFOBT screening has little or no difference on all-cause mortality.
No-screening vs annual gFOBT screening						
Colorectal cancer incidence	RR 0.86 (95% CI 0.72 to 1.03) based on data from 457 680 patients in eight studies. Follow-up 10.5–19.5 years.	26 per 1000	22 per 1000	4 fewer per 1000 (7 fewer to 1 more)	Moderate (serious imprecision)	Annual gFOBT screening probably has little or no difference on colorectal cancer incidence.
Colorectal cancer mortality	RR 0.69 (95% CI 0.56 to 0.86) based on data from 457 749 patients in eight studies. Follow-up 11.4–19.5 years.	10 per 1000	7 per 1000	3 fewer per 1000 (4 fewer to 1 fewer)	Moderate (serious imprecision)	Annual gFOBT screening probably slightly reduces colorectal cancer mortality.

Continued

Table 2 Continued

Outcome	Study results and measurements	Absolute effect estimates			Certainty in effect estimates	Plain text summary
		Comparator	Intervention	Difference (95% CI)		
All-cause mortality	RR 1.00 (95% CI 0.98 to 1.03) based on data from 457 750 patients in eight studies. Follow-up 11.4–19.5 years.	269 per 1000	269 per 1000	0 fewer per 1000 (5 fewer to 8 more)	Moderate (serious imprecision)	Annual gFOBT screening probably has little or no difference on all-cause mortality.
Biennial gFOBT vs sigmoidoscopy screening						
Colorectal cancer incidence	RR 0.80 (95% CI 0.71 to 0.91) based on data from 328 966 patients in eight studies. Follow-up 10.5–19.5 years.	28 per 1000	22 per 1000	6 fewer per 1000 (8 fewer to 3 fewer)	High	Sigmoidoscopy slightly reduces colorectal cancer incidence compared with biennial gFOBT screening.
Colorectal cancer mortality	RR 0.85 (95% CI 0.77 to 0.93) based on data from 329 003 patients in eight studies. Follow-up 11.4–19.5 years.	12 per 1000	10 per 1000	2 fewer per 1000 (3 fewer to 1 fewer)	High	Sigmoidoscopy slightly reduces colorectal cancer mortality compared with biennial gFOBT screening.
All-cause mortality	RR 0.99 (95% CI 0.97 to 1.01) based on data from 329 005 patients in eight studies. Follow-up 11.4–19.5 years.	438 per 1000	434 per 1000	4 fewer per 1000 (13 fewer to 4 more)	High	Sigmoidoscopy has little or no difference on all-cause mortality compared with biennial gFOBT screening.
Annual gFOBT vs sigmoidoscopy screening						
Colorectal cancer incidence	RR 0.89 (95% CI 0.73 to 1.09) based on data from 187 781 patients in five studies. Follow-up 10.5–18.0 years.	27 per 1000	24 per 1000	3 fewer per 1000 (7 fewer to 2 more)	Moderate (serious imprecision)	Sigmoidoscopy probably has little or no difference on colorectal cancer incidence compared with annual gFOBT screening.
Colorectal cancer mortality	RR 1.07 (95% CI 0.85 to 1.34) based on data from 187 819 patients in five studies. Follow-up 11.4–18.0 years.	8 per 1000	9 per 1000	1 more per 1000 (1 fewer to 3 more)	Moderate (serious imprecision)	Sigmoidoscopy probably has little or no difference on colorectal cancer mortality compared with annual gFOBT screening.
All-cause mortality	RR 0.99 (95% CI 0.96 to 1.02) based on data from 187 821 patients in five studies. Follow-up 11.4–18.0 years.	336 per 1000	333 per 1000	3 fewer per 1000 (13 fewer to 7 more)	Moderate (serious imprecision)	Sigmoidoscopy probably has little or no difference on all-cause mortality compared with annual gFOBT screening.
Biennial vs annual gFOBT screening						
Colorectal cancer incidence	RR 0.90 (95% CI 0.75 to 1.08) based on data from 172 249 patients in four studies. Follow-up 15.5–19.5 years.	28 per 1000	25 per 1000	3 fewer per 1000 (7 fewer to 2 more)	Moderate (serious imprecision)	Annual gFOBT screening probably has little or no difference on colorectal cancer incidence compared with biennial gFOBT screening.

Continued

Table 2 Continued

Outcome	Study results and measurements	Absolute effect estimates			Certainty in effect estimates	Plain text summary
		Comparator	Intervention	Difference (95% CI)		
Colorectal cancer mortality	RR 0.79 (95% CI 0.64 to 0.98) based on data from 172 324 patients in four studies. Follow-up 15.5–19.5 years.	12 per 1000	9 per 1000	3 fewer per 1000 (4 fewer to 0)	Moderate (serious imprecision)	Annual gFOBT screening probably slightly reduces colorectal cancer mortality, compared with biennial gFOBT screening.
All-cause mortality	RR 1.00 (95% CI 0.97 to 1.03) based on data from 172 324 patients in four studies. Follow-up 15.5–19.5 years.	438 per 1000	438 per 1000	0 fewer per 1000 (13 fewer to 13 more)	Moderate (serious imprecision)	Annual gFOBT screening probably has little or no difference on all-cause mortality compared with biennial gFOBT screening.

CI, confidence interval; gFOBT, guaiac faecal occult blood test; NMA, network meta-analysis; RR, relative risk.

0.01%) screening attenders in the trials reporting harms per two to five screening rounds, while it in the trial reporting harms per screening test was one (zero to one) per 10 000 screening tests (0.01%; 95% CI 0.00% to 0.01%) (figure 8). The risk of bleeding in the FIT trial was eight (3–14) per 10 000 (0.08%; 95% CI 0.03% to 0.14%) screening tests (figure 8). The risk of colorectal perforation in the sigmoidoscopy trials was three (one to four) per 10 000 (0.03%; 95% CI 0.01% to 0.04%) screening attenders, while for colonoscopy it was one (zero to three) per 10 000 (0.01%; 95% CI 0.00% to 0.03%) (figure 9). The risk of perforation in the gFOBT trials were one (one to two) per 10 000 (0.01%; 95% CI 0.01% to 0.02%) screening attenders in the trials reporting harms per two to five screening rounds, while it in the trial reporting harms per screening test was zero (zero to one) per 10 000 screening tests (0.00%; 95% CI 0.00% to 0.01%) (figure 9). The risk of perforation in the FIT trial was zero (zero to three) per 10 000 (0.00%; 95% CI 0.00% to 0.03%) screening tests (figure 9). The certainty of evidence for all screening interventions was downgraded to moderate due to risk of bias (online supplementary table 3A-B). The certainty of evidence for the gFOBT trials and FIT trial was downgraded further due to indirectness, with differences in the number of screening rounds (online supplementary table 3B and C).

Other physical harms and burdens

The mean risk of needing further workup due to findings at screening varied: 13% (95% CI 5% to 26%) in sigmoidoscopy trials, 7% (95% CI 7% to 8%) per screening test in the FIT trial, 5% (95% CI 5% to 5%) per screening test in gFOBT trials and 6% (95% CI 4% to 9%) per two to five gFOBT screening rounds (table 4 and supplementary table 3A-B). The confidence in the estimate of effect was downgraded to moderate certainty due to indirectness, resulting from differences in the number of screening rounds (gFOBT), and the differences in definitions of a positive screening test (online supplementary table 3A-B).

Surveillance of individuals with high-risk adenomas is recommended.[40] The trials did not report the findings of high-risk adenomas consistently, however, we referred to reported adenoma characteristics and the European Society of Gastrointestinal Endoscopy guidelines to estimate surveillance need.[40] We approximated those that will require surveillance as 1% (95% CI 1% to 2%) of screening attendees per two to five rounds with gFOBT screening, 2% (95% CI 2% to 3%) of screening attendees per FIT performed, 4% (95% CI 3% to 5%) of sigmoidoscopy screening attendees and 10% (95% CI 10% to 11%) of colonoscopy screening attendees (table 4 and supplementary table 3A-B). The certainty of evidence for all screening interventions was downgraded to moderate due to differences in reporting of the findings at screening or subsequent workup. The certainty of evidence from the gFOBT trials was further downgraded to low, due to differences in number of screening rounds. The certainty of evidence from the sigmoidoscopy trials were further downgraded to low, due to failure to report how information was obtained (online supplementary table 3A-B).

Other patient-important harms and burdens

All four sigmoidoscopy screening trials published reports on procedure-related pain,[41–44] where 16% (95% CI 10% to 22%) reported moderate-to-severe pain during the procedure (online supplementary figure 6). Only one of the colonoscopy trials[45] published a report on pain related to the procedure, where 21% (95% CI 19% to 22%) reported severe-to-moderate pain during the procedure, although no relation to sedation or air/CO2 insufflation was reported (online supplementary figure 6). The certainty of evidence of pain in sigmoidoscopy was downgraded to low certainty, due to probable selection bias in those who answered the questionnaires, as well as inconsistency between the trials (online supplementary table 3A). The certainty of evidence of pain in colonoscopy was high (online supplementary table 3B).

Table 3 Sex difference for sigmoidoscopy screening vs no-screening: relative and absolute NMA effect estimates for incidence and mortality in a 15-year perspective

Outcome	Study results and measurements	Absolute effect estimates			Certainty in effect estimates	Plain text summary
		Comparator	Intervention	Difference (95% CI)		
Colorectal cancer incidence, women	RR 0.86 (95% CI 0.79 to 0.93) based on data from 231 561 patients in four studies. Follow-up 10.5–17.1 years.	20 per 1000	17 per 1000	3 fewer per 1000 (4 fewer to 1 fewer)	High	Sigmoidoscopy slightly reduces colorectal cancer incidence in women.
Colorectal cancer incidence, men	RR 0.74 (95% CI 0.69 to 0.80) based on data from 226 424 patients in four studies. Follow-up 10.5–17.1 years.	29 per 1000	21 per 1000	8 fewer per 1000 (9 fewer to 6 fewer)	High	Sigmoidoscopy slightly reduces colorectal cancer incidence in men.
Colorectal cancer mortality, women	RR 0.86 (95% CI 0.73 to 1.01) based on data from 253 466 patients in four studies. Follow-up 14.8–19.5 years.	8 per 1000	7 per 1000	1 fewer per 1000 (2 fewer to 0)	High	Sigmoidoscopy has little or no difference on colorectal cancer mortality in women.
Colorectal cancer mortality, men	RR 0.67 (95% CI 0.61 to 0.75) based on data from 245 245 patients in four studies. Follow-up 14.8–19.5 years.	12 per 1000	8 per 1000	4 fewer per 1000 (5 fewer to 3 fewer)	High	Sigmoidoscopy slightly reduces colorectal cancer mortality in men.
All-cause mortality, women	RR 0.99 (95% CI 0.95 to 1.03) based on data from 136 301 patients in two studies. Follow-up 14.8–17.1 years.	168 per 1000	166 per 1000	2 fewer per 1000 (8 fewer to 5 more)	High	Sigmoidoscopy has little or no difference on all-cause mortality in women.
All-cause mortality, men	RR 0.99 (95% CI 0.95 to 1.03) based on data from 132 525 patients in two studies. Follow-up 14.8–17.1 years.	250 per 1000	248 per 1000	2 fewer per 1000 (12 fewer to 8 more)	High	Sigmoidoscopy has little or no difference on all-cause mortality in men.

CI, confidence interval; NMA, network meta-analysis; RR, relative risk.

We identified four reports on the psychological impact of a positive screening test, two from sigmoidoscopy,[46 47] and one from each gFOBT[48 49] and FIT.[47] One report on sigmoidoscopy screening[46] used the short version of the Spielberger State-Trait Anxiety Inventory (STAI)[50] to ask participants if they were worried about bowel cancer before and 3 months after sigmoidoscopy screening, and reported no significant psychological harms associated with positive screening results. One report on gFOBT screening[48] measured anxiety using the original STAI, and reported that anxiety scores in a sample of 100 screening test false-positive patients were highest after the notification of a positive test, fell after a negative workup colonoscopy, and subsequently remained low. There were no data on the individuals who had a positive test, but did not attend the workup colonoscopy.

Another report on gFOBT screening[49] measured worry at different time points during the screening process by using a questionnaire where the screening attenders reported their worry on a five-point scale ranging from 'not at all' to 'extremely'. Sixty per cent reported to be extremely or very worried after receiving a positive gFOBT screening test result, an increase of 44 percentage points from when first receiving the invitation to screening. Concurrently, 15% reported negative effects on daily life 'to a great deal' when receiving the positive test result, compared with 5% when receiving the invitation to screening.

The most recent study, on sigmoidoscopy and FIT screening,[47] reported no significant increase in anxiety and depression on the Hospital Anxiety and Depression Scale[51] after a positive result in either sigmoidoscopy or

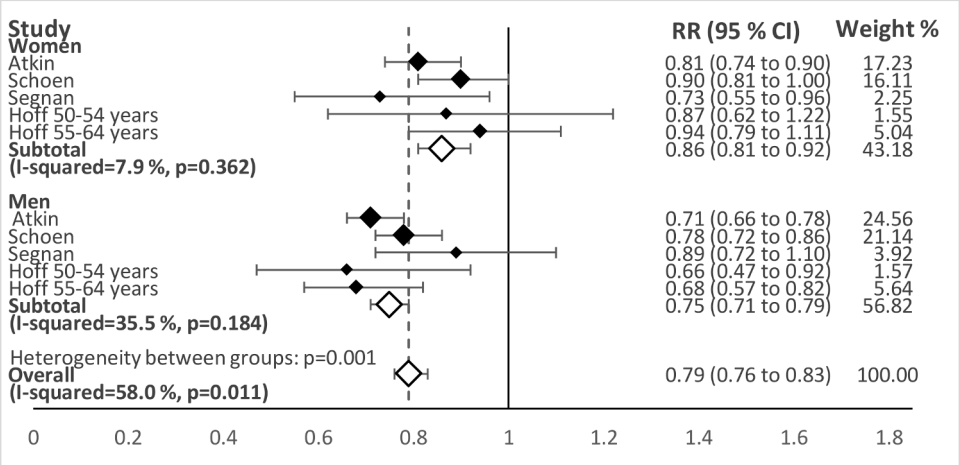

Figure 6 Sex differences on colorectal cancer incidence with sigmoidoscopy screening compared with no-screening. RR, relative risk.

FIT, neither before or after the workup colonoscopy, regardless of colonoscopy result.

We also searched for data on absence for work to prepare for, attend and recover after the screening, as decided a priori by the guideline panel, but no data were identified in the included randomised trials.

DISCUSSION

Statement of principal findings

Screening with gFOBT or sigmoidoscopy slightly reduced colorectal cancer mortality in a 15-year perspective, based on high certainty evidence. Neither gFOBT nor sigmoidoscopy screening, however, had any effect on all-cause mortality. The absolute effects will depend on the baseline risk of the screening attenders, thus in the trials the absolute effect was one less colorectal cancer death per 1000 (0.1%) individuals screened with gFOBT biennially, and three fewer colorectal cancer deaths per 1000 (0.3%) individuals screened with gFOBT annually or once-only sigmoidoscopy.

Sigmoidoscopy screening also slightly reduced colorectal cancer incidence, based on high certainty evidence, where the absolute effect observed in the trials was six fewer colorectal cancer cases per 1000 (0.6%) individuals screened in a 15-year perspective. We found no significant difference between annual gFOBT and sigmoidoscopy screening on colorectal cancer incidence, but the certainty of evidence is moderate, as annual gFOBT has been evaluated in only one trial where rate of events is low. Biennial gFOBT had no effect on colorectal cancer incidence.

Compared with annual or biennial gFOBT, or no-screening, sigmoidoscopy is the most effective method for decreasing both colorectal cancer mortality and incidence in a 15-year perspective. However, sigmoidoscopy has a greater relative effect in men than in women: five fewer colorectal cancer cases and three fewer colorectal cancer deaths per 1000 (0.5% and 0.3%) screened individuals in men compared with in women. The reasons behind the greater relative effect in men than in

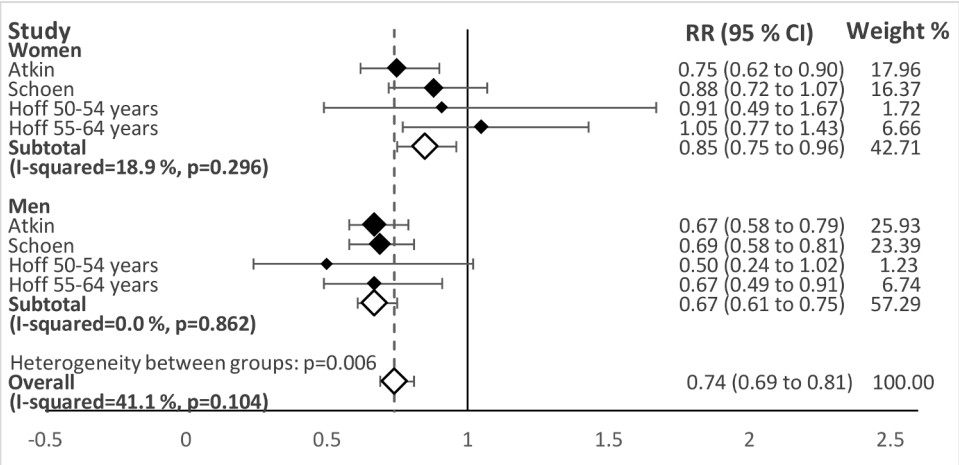

Figure 7 Sex differences on colorectal cancer mortality with sigmoidoscopy screening compared with no-screening. RR, relative risk.

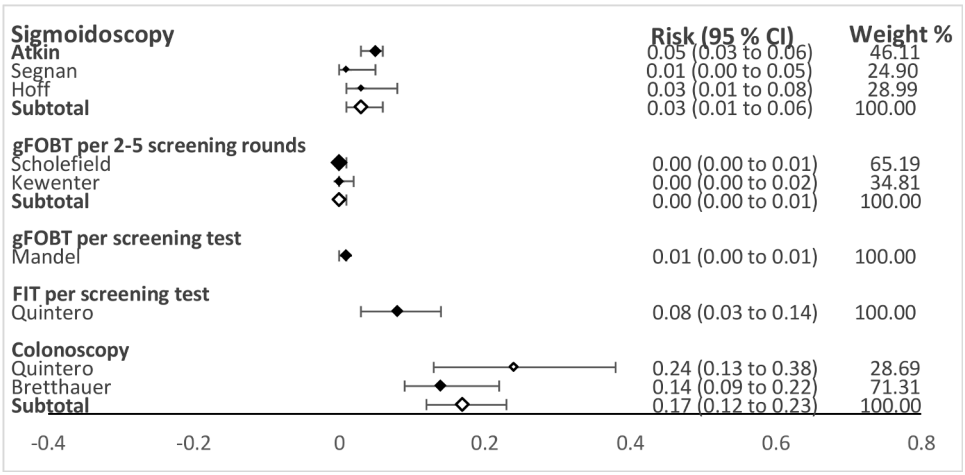

Figure 8 Risk of bleeding requiring hospitalisation after screening and workup procedure shown as percentage of screening attenders with 95% CIs, unless otherwise mentioned. gFOBT, guaiac faecal occult blood test; FIT, faecal immunochemical test.

women is unknown. Sigmoidoscopy screening focuses on the detection of adenomas, one of the precursors to colorectal cancer.[2 52 53] Men have a higher risk of developing adenomas, and colorectal cancers in women may more frequently develop from a different pathway, such as sessile serrated adenomas.[54] With increasing evidence that there is a difference in the relative effect of sigmoidoscopy screening between men and women, this should be studied further.

The certainty of the evidence on harms and burdens reported in the randomised trials was downgraded mainly due to high risk of bias, as none of the trials reported how the data were collected. Bleeding requiring hospitalisation and colorectal perforations after screening or subsequent workup occurred in between one and three per 10 000 (0.01% to 0.03%) individuals screened. Moderate-to-severe pain was reported by approximately one in five (16%–21% dependent on screening method) individuals undergoing endoscopic procedures. Screening attenders receiving a positive screening test experienced immediate anxiety, but no sustained psychological effects are shown. However, information on individuals choosing not to attend the workup procedure is not found.

Strengths and limitations of the study

This review has several strengths: first, the review was conducted based on an a priori protocol, based on the Cochrane and GRADE approaches.[19–23] Second, outcomes were informed by input from professionals and patient partners in the BMJ Rapid Recommendations guideline panel. Third, the study is based on a comprehensive systematic search of several databases, and it is unlikely that we have missed any ongoing or previously performed trials. Finally, this review, in addition to showing relative effects of the screening interventions, also quantifies the absolute risks, as compared with the average control population in the studies, in a 15-year perspective. This enables the reader to interpret the effects more easily.

The major limitation of this study is that we only look at harms and burdens of the screening interventions in randomised trials. As none of the randomised trials are designed for collecting data on the harms and burdens

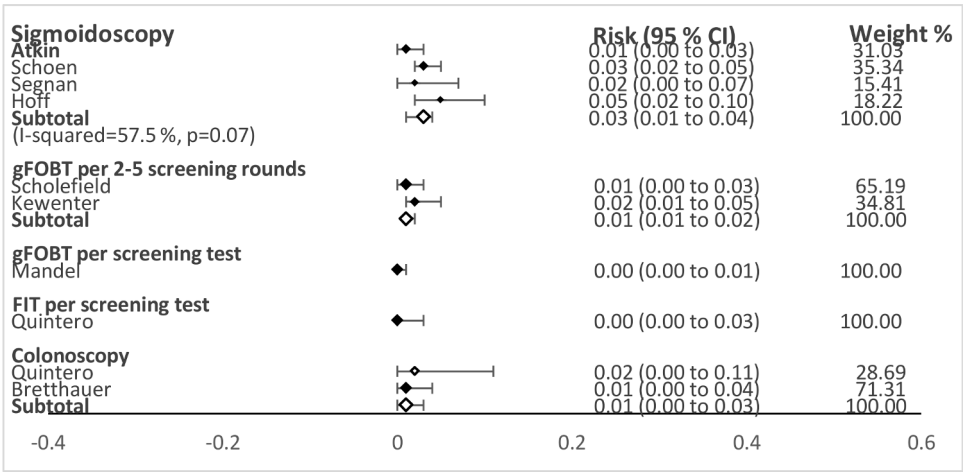

Figure 9 Risk of colorectal perforation after screening and workup procedure shown as percentage of screening attenders with 95% CIs, unless otherwise mentioned. gFOBT, guaiac faecal occult blood test; FIT, faecal immunochemical test.

Table 4 Harms and burdens

Screening method	Study	Met to screening	Workup procedure	Surveillance endoscopy*	Death <30 days of procedure†	Death <30 days of surgery	Major complications‡†	Miscellaneous§†	Pain¶
Sigmoidoscopy	Atkin[41 46]	40674	2131	1745	7	4	3	192	7947
			5%	4%	0.02%	0.01%	0.01%	0.47%	20%
	Schoen[58 59]	64658	15150	2153**	NR	NR	NR	NR	232
			23%	3%					19%
	Segnan[43]	9911	832	395¶¶	NR	NR	NR	90	1833
			8%	4%				0.91%	20%
	Hoff[44 71]	12960	2639	545**	NR	0	2	79	283
			20%	4%		0.00%	0.02%	0.61%	6%
	Mean		**13%**	**4%**	**0.02%**	**0.01%**	**0.01%**	**0.68%**	**16%**
	(95% CI)		**(5% to 26%)**	**(3% to 5%)**	**(0.01% to 0.04%)**	**(0.00% to 0.02%)**	**(0.00% to 0.02%)**	**(0.41% to 0.90%)**	**(10% to 22%)**
gFOBT per 2–5 screening rounds	Scholefield (3–5 rounds)[34 35]	44838	2212	710	0	5	0	1	NA
			5%	2%	0.00%	0.01%	0.00%	0.00%	
	Kronborg (5 rounds)[36]	20672	986	270‡‡	NR	NR	NR	NR	NA
			5%	1%					
	Kewenter (2–3 rounds)[37 68]	23916	2108	305‡‡	0	0	0	14	NA
			9%	1%	0.00%	0.00%	0.00%	0.06%	
	Mean		**6%**	**1%**	**0.00%**	**0.01%**	**0.00%**	**0.01%**	
	(95% CI)		**(4% to 9%)**	**(1% to 2%)**	**NA**	**(0.00% to 0.01%)**	**NA**	**(0.01% to 0.02%)**	
gFOBT per screening test	Mandel[38]	202 116§§	17008	NR	NR	NR	NR	NR	NA
			8%						
	Pitkaniemi[39]	301 900§§	10743	NR	NR	NR	NR	NR	NA
			4%						
	Mean		**5%**						
	(95% CI)		**(5% to 5%)**						
FIT per screening test	Quintero[69]	10611	767	252**	NR	NR	2	NR	NA
			7%	2%			0.02%		
	Mean		**7%**	**2%**			**0.02-%**		
	(95% CI)		**(7% to 8%)**	**(2% to 3%)**			**(0.00% to 0.07%)**		

Continued

Table 4 Continued

Screening method	Study	Met to screening	Workup procedure	Surveillance endoscopy*	Death <30 days of procedure†	Death <30 days of surgery	Major complications‡†	Miscellaneous§†	Pain¶
Colonoscopy	Quintero[72]	5059	NA	493**	NR	NR	11	NR	NR
				10%			0.22%		
	Bretthauer[70]	12574	NA	1304††	0	NR	0	51	749
				10%	0.00%		0.00%	0.41%	21%
	Mean			**10%**	**0.00%**		**0.02%**	**0.41%**	**21%**
	(95% CI)			**(10% to 11%)**	**NA**		**(0.00% to 0.05%)**	**(0.32% to 0.50%)**	**(19% to 22%)**

All numbers are number of screening participants, and percentages are calculated as percentage of participants met to screening, unless otherwise stated.
*According to ESGE guidelines,[40] unless otherwise stated.
†Within 30 days of screening or diagnostic workup.
‡Bleeding, perforation and death excluded. Sigmoidoscopy: two myocardial infarctions, one pulmonary embolus, one burnt serosa syndrome and one fever of unknown cause. FIT: two individuals with hypotension or bradycardia. Colonoscopy: 10 individuals with hypotension or bradycardia, one desaturation.
§Includes snare entrapment, vasovagal reactions, glutaraldehyde colitis and other events not requiring hospitalisation.
¶Per cent of those responded who reported moderate to severe pain during the procedure.
**Advanced adenoma.
††High-risk adenomas: advanced adenoma, or ≥3 adenomas.
‡‡Adenomas >10 mm.
§§Total number of screening tests performed (not number of individuals).
¶¶High-risk adenomas, 27 with low-risk distal adenomas with proximal polyps not sent to histology and 11 colorectal cancers endoscopically treated.
CI, confidence interval; ESGE, European Society of Gastrointestinal Endoscopy; FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test; NA, not applicable; NR, not reported.

and do not report how data on harms and burdens were obtained, observational trials might provide further information on these outcomes. In addition, the absolute effects calculations are based on the mean risk of colorectal cancer incidence and mortality in the control groups of the different trials, which varies between the different trials. This might be due to the different calendar times at which the trials were performed, in addition to differences between the control groups of the different trials. All absolute risk reduction estimates assume that all individuals have mean risk. This is a strong assumption in the individual perspective, but represent the mean absolute effect in our target population of healthy individuals aged 50–79 years.

Findings in relation to other studies

Prior reviews show that sigmoidoscopy screening reduces colorectal cancer incidence, while both sigmoidoscopy and gFOBT reduce colorectal cancer mortality.[4–7] This is the first review that includes follow-up from three of the major sigmoidoscopy trials exceeding 14.8 years,[8–10] and we show that there is sustained effect of once-only sigmoidoscopy screening even 14.8 years after screening. This is also the first review that performs a network meta-analysis comparing the different screening test against one another with this long follow-up.

In addition, this is the first meta-analysis assessing the subgroup effect of sigmoidoscopy screening by sex with data from all four major sigmoidoscopy trials after 14.8 years of follow-up, demonstrating that there is a greater relative effect of reduction of both colorectal cancer incidence and mortality in men than in women.

Implications for clinicians and policy makers

Our review shows that sigmoidoscopy screening slightly reduces colorectal cancer incidence even 15 years after a once-only screening. Sigmoidoscopy, annual and biennial gFOBT all slightly reduce colorectal cancer mortality in the same time perspective. Sigmoidoscopy is likely to be more effective in men than in women both for colorectal cancer incidence and mortality. None of the screening interventions show effect on all-cause mortality. These results show that the relative effect of once-only sigmoidoscopy screening is maintained as long as 15 years after screening. Most guidelines today recommend rescreening 5–10 years after initial screening. This may now be safely extended to 15 years.

Harms and burdens were reported with large variation. The frequency of testing (annual or biennial for faecal blood tests) is important in the evaluation of possible harms and need of surveillance, as more frequent testing is likely to increase the rate of harms. The need for future surveillance reported in this study must be viewed critically for implications in contemporary practice, in particularly for gFOBT, where studies used sigmoidoscopy and barium contrast enemas, instead of colonoscopy, as the primary workup strategy after a positive screening test.

All trials on colorectal cancer screening mainly have participants of European origin, and there is paucity of data for other ethnicities.

Unfortunately, there are no reports on long-term effects on colorectal cancer incidence and mortality of FIT and colonoscopy. Colonoscopy and FIT both have higher sensitivity than gFOBT and colonoscopy, and are therefore likely to have a larger effect on incidence and mortality.[55] However, these benefits must be weighed against increased harms and burdens such as more individuals in need of colonoscopy surveillance.

This review supported the development of an evidence-based clinical practice guideline, as reflected in the accompanying Rapid recommendations guideline.[16]

Author affiliations
[1]Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, Oslo, Norway
[2]Clinical Effectiveness Research Group, Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway
[3]Frontier Science Foundation, Boston, Massachusetts, USA
[4]Veterans Affairs Medical Center, White River Junction, Vermont, USA
[5]The Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, USA
[6]University of Connecticut Health Center, Farmington, Connecticut, USA
[7]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
[8]Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
[9]Department of Medicine, Lovisenberg Diaconal Hospital, Oslo, Norway
[10]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA
[11]Vårdcentralen Värmlands Nysäter & Centre for Clinical Research, County Council of Värmland, Karlstad, Sweden

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Contributors HCJ drafted the protocol and the first draft of the review. HCJ, LMH and JCA performed data extraction. HCJ and LMH assessed risk of bias of included studies. HCJ and LE performed the statistical analyses. PV and LE supervised the study. HCJ, LMH, JCA, LL, PV and LE participated in writing the manuscript, interpretation of results and approval of the final version of the review. Corresponding author HCJ is the guarantor.

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ORCID iDs
Henriette C Jodal http://orcid.org/0000-0001-6957-9469
Lise M Helsingen http://orcid.org/0000-0002-2055-3978

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Appendix 1: Search terms and strategies

Medline (faecal occult blood) search strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1	exp Colorectal Neoplasms/
2	exp Colonic Neoplasms/
3	exp Rectal Neoplasms/
4	((colorectal* or CRC or colon* or bowel* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or tumor* or tumour or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*)).mp.
5	1 or 2 or 3 or 4
6	exp Occult Blood/
7	exp Immunochemistry/
8	(faecal or fecal or feces or faeces or gFOBT or FOBT or FOB or FIT or haemoccult or hemoccult or sensa or heamoccultsensa or hemocare or hema screen or hemascreen or hemacheck or hema check or hemawipe or hema wipe or hemofec or hemofecia or fecatest or fecatwin or coloscreen or seracult or ez?detect or colocare or flexsure or hemmoquant or immocare or hemochaser or bayer detect or hemeselect or immudia or monohaem or insure or hemodia or instant?view or immocare or magstream or guaiac or occult blood or (stool adj3 occult) or (gaiac* adj2 smear*)).mp.
9	((((immunochemical* adj3 (test* or screen* or diagn*)) or immunologic*) adj3 (test* or screen* or diagn*)) or enzyme or EIA or assay or RPHA or latex or agglutin* or monocl* or polyclo*).mp.
10	6 or 7 or 8 or 9
11	exp Mass Screening/
12	exp Population Surveillance/
13	(screen* or test* or (population* adj2 surveillance) or (early adj3 detect*) or (early adj3 prevent*)).mp.
14	11 or 12 or 13
15	5 and 10 and 14
16	randomized controlled trial.pt.
17	controlled clinical trial.pt.
18	randomized.ab.
19	placebo.ab.
20	clinical trial.sh.
21	randomly.ab.
22	trial.ti.
23	16 or 17 or 18 or 19 or 20 or 21 or 22
24	15 and 23
25	((canin* or dog* or rodent* or rat* or mouse or mice* or animal* or mammal* or mice* or bird* or fish* or trout*).ti,ab. or Animals/) not Humans/
26	24 not 25
27	limit 26 to yr="2012 -Current"

Medline (flexible sigmoidoscopy) search strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1	humans.sh.
2	humans/
3	exp Colorectal Neoplasms/
4	exp Colonic Neoplasms/

5	exp Rectal Neoplasms/
6	((colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*)).mp.
7	3 or 4 or 5 or 6
8	exp Endoscopy, Gastrointestinal/
9	exp Colonoscopy/
10	exp Sigmoidoscopy/
11	exp Proctoscopy/
12	(endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or COL or SIG or FSIG or (flex* adj3 sig*)).mp.
13	8 or 9 or 10 or 11 or 12
14	exp Mass Screening/
15	exp Population Surveillance/
16	(screen* or test* or (population* adj2 surveillance) or (early adj3 detect*) or (early adj3 prevent*)).mp.
17	14 or 15 or 16
18	7 and 13 and 17
19	randomized controlled trial.pt.
20	controlled clinical trial.pt.
21	randomized.ab.
22	placebo.ab.
23	clinical trial.sh.
24	randomly.ab.
25	trial.ti.
26	19 or 20 or 21 or 22 or 23 or 24 or 25
27	18 and 26
28	((canin* or dog* or rodent* or rat* or mouse or mice* or animal* or mammal* or mice* or bird* or fish* or trout*).ti,ab. or Animals/) not Humans/
29	27 not 28
30	limit 29 to yr="2012 -Current"

EMBASE (faecal occult blood) search strategy

Embase Classic+Embase <1947 to 2018>

1	exp colorectal tumor/
2	exp colorectal cancer/
3	exp colorectal carcinoma/
4	exp colorectal adenoma/
5	exp colon tumor/
6	exp colon cancer/
7	exp colon carcinoma/
8	exp colon adenoma/
9	exp colon adenocarcinoma/
10	exp rectum tumor/
11	exp rectum cancer/
12	exp rectum carcinoma/
13	exp rectum adenoma/
14	((colorectal* or CRC or colon or colonic or bowel* or intestine or large intestine or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*)).m_titl.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	exp occult blood/

17	exp feces analysis/
18	exp immunochemistry/
19	(faecal or fecal or feces or faeces or gFOBT or FOBT or FOB or FIT or haemoccult or hemoccult or sensa or heamoccultsensa or hemocare or hema screen or hemascreen or hemacheck or hema check or hemawipe or hema wipe or hemofec or hemofecia or fecatest or fecatwin or coloscreen or seracult or ez?detect or colocare or flexsure or hemmoquant or immocare or hemochaser or bayer detect or hemeselect or immudia or monohaem or insure or hemodia or instant?view or immocare or magstream or guaiac or occult blood or (stool adj3 occult) or (gaiac* adj2 smear*)).mp.
20	((((immunochemical* adj3 (test* or screen* or diagn*)) or immunologic*) adj3 (test* or screen* or diagn*)) or enzyme or EIA or assay or RPHA or latex or agglutin* or monocl* or polyclo*).mp.
21	16 or 17 or 18 or 19
22	exp mass screening/
23	exp health survey/
24	(screen* or test* or (population* adj2 surveillance) or (early adj3 detect*) or (early adj3 prevent*)).m_titl.
25	21 or 22 or 23
26	15 and 21 and 25
27	randomized controlled trial/
28	randomization/
29	controlled study/
30	multicenter study/
31	phase 3 clinical trial/
32	phase 4 clinical trial/
33	27 or 28 or 29 or 30 or 31 or 32
34	26 and 33
35	((canin* or dog* or rodent* or rat* or mouse or mice* or animal* or mammal* or mice* or bird* or fish* or trout* or nonhuman*).ti,ab. or exp Animal/ or Nonhuman/) not human/
36	34 not 35
37	limit 36 to yr="2012 -Current"

EMBASE (Flexible sigmoidoscopy) search strategy

Embase Classic+Embase <1947 to 2018>

1	exp colorectal cancer/
2	exp colorectal tumor/
3	exp colorectal carcinoma/
4	exp colorectal adenoma/
5	exp colon carcinoma/
6	exp colon cancer/
7	exp colon adenoma/
8	exp colon adenocarcinoma/
9	exp colon tumor/
10	exp rectum cancer/
11	exp rectum tumor/
12	exp rectum carcinoma/
13	exp rectum adenoma/
14	((colorectal* or CRC or colon or colonic or bowel* or intestine or large intestine or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*)).m_titl.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	exp gastrointestinal endoscopy/

17	exp colonoscopy/
18	exp sigmoidoscopy/
19	exp rectoscopy/
20	(endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or COL or SIG or FSIG or (flex* adj3 sig*)).mp.
21	16 or 17 or 18 or 19 or 20
22	exp mass screening/
23	exp health survey/
24	(screen* or test* or (population* adj2 surveillance) or (early adj3 detect*) or (early adj3 prevent*)).m_titl.
25	22 or 23 or 24
26	15 and 21 and 25
27	randomized controlled trial/
28	randomization/
29	controlled study/
30	multicenter study/
31	phase 3 clinical trial/
32	phase 4 clinical trial/
33	27 or 28 or 29 or 30 or 31 or 32
34	26 and 33
35	((canin* or dog* or rodent* or rat* or mouse or mice* or animal* or mammal* or mice* or bird* or fish* or trout* or nonhuman*).ti,ab. or exp Animal/ or Nonhuman/) not human/
36	34 not 35
37	limit 36 to yr="2012 -Current"

The Cochrane Library (faecal occult blood) search strategy

#1	[mh "Colorectal Neoplasms"]
#2	[mh "Colonic Neoplasms"]
#3	[mh "Rectal Neoplasms"]
#4	(colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*):ti,ab,kw
#5	#1 or #2 or #3 or #4
#6	[mh "Occult Blood "]
#7	[mh Immunochemistry]
#8	(faecal or fecal or feces or faeces or gFOBT or FOBT or FOB or FIT or haemoccult or hemoccult or sensa) or (heamoccultsensa or hemocare or hema screen or hemascreen or hemacheck or hema check or hemawipe or hema wipe) or (hemofec or hemofecia or fecatest or fecatwin or coloscreen or seracult or ez?detect or colocare or flexsure) or (hemmoquant or immocare or hemochaser or bayer detect or hemeselect or immudia or monohaem or insure or hemodia or instant?view or magstream or guaiac or occult blood) or (stool near/3 occult) or (gaiac* near/2 smear*):ti,ab,kw
#9	(immunochemical* near/3 (test* or screen* or diagn*)) or (immunologic* near/3 (test* or screen* or diagn*)) or (enzyme or EIA or assay or RPHA or latex or agglutin* or monocl* or polyclo*):ti,ab,kw
#10	(#6 or #7 or #8 or #9)
#11	[mh "Mass Screening"]
#12	[mh "Population Surveillance"]
#13	(screen* or test*) or (population* near/2 surveillance) or (early near/3 detect*) or (early near/3 prevent*):ti,ab,kw
#14	(#11 or #12 or #13)
#15	(#5 and #10 and #14) Publication Year from 2012 to 2018

The Cochrane Library (flexible sigmoidoscopy) search strategy

#1	[mh "Colorectal Neoplasms"]
#2	[mh "Colonic Neoplasms"]
#3	[mh "Rectal Neoplasms"]
#4	(colorectal* or CRC or colon* or bowel* or intestine* or large intestine* or rectal or rectum or sigmoid or anal or anus) and (cancer or neoplasm* or malign* or tumor* or tumour* or carcinom* or sarcom* or adenocarcinom* or adeno?carcinom* or adenom* or lesion*):ti,ab,kw
#5	#1 or #2 or #3 or #4
#6	[mh Endoscopy]
#7	[mh Colonoscopy]
#8	[mh Sigmoidoscopy]
#9	[mh Proctoscopy]
#10	(endoscop* or proctoscop* or colonoscop* or sigmoidoscop* or rectosigmoidoscop* or proctosigmoidoscop* or COL or SIG or FSIG) or (flex* near/3 sig*):ti,ab,kw
#11	#6 or #7 or #8 or #9 or #10
#12	[mh "Mass Screening"]
#13	[mh "Population Surveillance"]
#14	(screen* or test*) or (population* near/2 surveillance) or (early near/3 detect*) or (early near/3 prevent*):ti,ab,kw
#15	#12 or #13 or #14
#16	#5 and #11 and #15 Publication Year from 2012 to 2018

Appendix 2: Reporting checklist (PRISMA-NMA)

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	5-6

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	6
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	6-7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	6-7
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses;	6-7

Jodal HC, *et al. BMJ Open* 2019; 9:e032773. doi: 10.1136/bmjopen-2019-032773

		• *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	12
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	11+ Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	Summary from each intervention provided: 13-21
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	13-14
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	13-21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	13-21
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied,*	19-28

		alternative choice of prior distributions for Bayesian analyses, and so forth).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	28-29
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	29
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	30
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	32

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicate wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix 3: Summary of risk of bias assessments for the included trials

Atkin 2002

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Atkin 2017.
Allocation concealment (selection bias)		Low risk	See Atkin 2017.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Atkin 2017.
	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	Baseline questionnaire complete in 98% of screened persons. Follow-up questionnaire complete in 91% of screened persons.
	Harms and burdens	High risk	It is not described how information on harms and burdens were obtained.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Atkin 2010

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Atkin 2017.
Allocation concealment (selection bias)		Low risk	See Atkin 2017.

Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Atkin 2017.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	Six people in each group could not be traced. 658 people had emigrated.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Atkin 2017

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		Low risk	Sequentially numbered randomisation was done centrally in blocks of 12 and with the added constraint of no more than three consecutive allocations to one group within or across blocks.
Allocation concealment (selection bias)		Low risk	Central randomisation procedure.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	Outcomes were obtained from or confirmed by public registries. A second analysis as CRC as an underlying cause of death was obtained after blinded verification of death certificates by an independent expert coder who had access to clinical information when available.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	The NHSCR was unable to trace six people in the control group and six in the intervention group, two of whom were screened. A further 234 (<1%) in the intervention group and 451 (<1%) in the control group emigrated.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threaths to validity detected.

Bretthauer 2016

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	Randomisation of individuals directly from the Population Registries. Household randomisation.
Allocation concealment (selection bias)		Low risk	Central randomisation procedure.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Harms and burdens	High risk	It is not described how information on harms and burdens were obtained.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Gondal 2003

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Holme 2018.
Allocation concealment (selection bias)		Low risk	See Holme 2018.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Holme 2018.
	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	See Holme 2018.

	Harms and burdens	High risk	It is not described how information on harms and burdens were obtained.
	Incidence/mortality	Low risk	All relevant outcomes were reported.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Hardcastle 1996

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		Low risk	See Scholefield 2002.
Allocation concealment (selection bias)		Low risk	See Scholefield 2002.
	Incidence/mortality	Low risk	See Scholefield 2002.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
	Incidence/mortality	Low risk	See Scholefield 2002.
Incomplete data (attribution bias)	Harms and burdens	Low risk	Number of patients and size of adenomas at endoscopic procedures described.
	Incidence/mortality	Low risk	See Scholefield 2002.
Selective reporting (reporting bias)	Harms and burdens	Low risk	See Scholefield 2002.
Other bias		Low risk	See Scholefield 2002.

Hoff 2009

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Holme 2018.
Allocation concealment (selection bias)		Low risk	See Holme 2018.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Holme 2018.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	1196 people were lost to follow-up due to emigration.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threahs to validity detected.

Holme 2014

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Holme 2018.
Allocation concealment (selection bias)		Low risk	See Holme 2018.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Holme 2018.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	385 individuals in the control group, and 33 individuals in the screening group not traceable due to emigration. 3 individuals in the control group not traceable in the population registry.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes reported.
Other bias		Low risk	No other threats to validity detected.

Holme 2017

Bias	Outcomes	Author's judgement	Support for judgement

Random sequence generation (selection bias)		Low risk	See Holme 2018, Schoen 2012 and Segnan 2011.
Allocation concealment (selection bias)		Low risk	See Holme 2018, Schoen 2012 and Segnan 2011.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Holme 2018, Schoen 2012 and Segnan 2011.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	See Holme 2018, Schoen 2012 and Segnan 2011.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	See Holme 2018, Schoen 2012 and Segnan 2011.
Other bias		Low risk	See Holme 2018, Schoen 2012 and Segnan 2011.

Holme 2018

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	Randomisation was done independently according to social security number by Statistics Norway.
Allocation concealment (selection bias)		Low risk	Central randomisation process.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	Outcomes were obtained from public registries by a person not involved in the trial.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	478 individuals in the control group, and 53 individuals in the screening group not traceable due to emigration. 3 individuals in the control group not traceable in the population registry.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Jørgensen 2002

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Kronborg 2004.
Allocation concealment (selection bias)		Low risk	See Kronborg 2004.

Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Kronborg 2004.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	See Kronborg 2004.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	See Kronborg 2004.
Other bias		Low risk	See Kronborg 2004.

Kewenter 1994

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		High risk	See Lindholm 2008.
Allocation concealment (selection bias)		Low risk	See Lindholm 2008.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Lindholm 2008.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	See Lindholm 2008.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	See Lindholm 2008.
Other bias		Low risk	See Lindholm 2008.

Kewenter 1996

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		High risk	See Lindholm 2008.
Allocation concealment (selection bias)		Low risk	See Lindholm 2008.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Harms and burdens	High risk	Report before completion of screening rounds.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	See Lindholm 2008.

Kirkøen 2016

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		High risk	Randomisation done through population registry, however the groups who chose to answer the questionnaires are different.
Allocation concealment (selection bias)		Low risk	Central randomisation procedure.
Blinding (performance and detection bias)	Harms and burdens	High risk	Questionnaires at baseline was delivered at the same time as invitation to screening, this may have affected the baseline results.
Incomplete data (attribution bias)	Harms and burdens	High risk	Low response-rate (42 % in intervention groups, 35 % in control group).
Selective reporting (reporting bias)	Harms and burdens	Low risk	Due to it being an ongoing trial, few outcomes are reported at this time.
Other bias		Low risk	No other threats to validity detected.

Kronborg 1996

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Kronborg 2004.
Allocation concealment (selection bias)		Low risk	See Kronborg 2004.
	Incidence/mortality	Low risk	See Kronborg 2004.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	See Kronborg 2004.

	Harms and burdens	Low risk	Complete number with positive tests reported.
	Incidence/mortality	Low risk	See Kronborg 2004.
Selective reporting (reporting bias)	Harms and burdens	High risk	No data on other harms and burdens than number needed to go to further diagnostic work-up reported.
Other bias		Low risk	See Kronborg 2004.

Kronborg 2004

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	Central block randomisation procedure based on social security number.
Allocation concealment (selection bias)		Low risk	Central randomisation procedure.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	The investigators were unaware of the trial allocation during the assessment of death certificates.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	All participants were followed until death or end of study.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Larsen 2002

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		High risk	See Holme 2018. Unknown whether the randomisation was maintained in this subgroup study.
Allocation concealment (selection bias)		Low risk	See Holme 2018.

Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Harms and burdens	Low risk	High response rate to the questionnaires (92 %).
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threaths to validity detected.

Lindholm 1997

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		High risk	See Lindholm 2008.
Allocation concealment (selection bias)		Low risk	Central randomisation procedure based on the population registry.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Harms and burdens	High risk	Great variation in response rates to questionnaires and interviews in the different groups.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Lindholm 2008

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		High risk	Random sequence generation not described.
Allocation concealment (selection bias)		Low risk	Central randomisation procedure based on the population registry.

	Incidence/mortality	Low risk	Colorectal cancer diagnosis and cause of death obtained from public registries. In cases of uncertainty of cause of death, an independent reviewer who was blinded to study group allocation evaluated case records.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
	Incidence/mortality	Low risk	All individuals could be traced at follow-up except for 532 emigrants.
Incomplete data (attribution bias)	Harms and burdens	Low risk	Number of patients and size of adenomas at endoscopic procedures described.
	Incidence/mortality	Low risk	All relevant outcomes were reported.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Mandel 1993

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		Low risk	See Shaukat 2013.
Allocation concealment (selection bias)		Low risk	See Shaukat 2013.
	Incidence/mortality	Low risk	See Shaukat 2013.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.

	Incidence/mortality	Low risk	See Mandel 2000.
Incomplete data (attribution bias)	Harms and burdens	High risk	It is not described how information on harms and burdens were obtained.
	Incidence/mortality	Low risk	See Mandel 2000.
Selective reporting (reporting bias)	Harms and burdens	Low risk	See Mandel 2000.
Other bias		Low risk	See Mandel 2000.

Mandel 1999

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		Low risk	See Shaukat 2013.
Allocation concealment (selection bias)		Low risk	See Shaukat 2013.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Shaukat 2013.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	See Mandel 2000.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	See Mandel 2000.
Other bias		Low risk	See Mandel 2000.

Mandel 2000

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		Low risk	See Shaukat 2013.
Allocation concealment (selection bias)		Low risk	See Shaukat 2013.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Shaukat 2013.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	Death certificates obtained for 99.9% of participants.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.

Other bias	Low risk	Participants recruited among volunteers.

Miller 2018

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	Volunteers who responded to an invitation through mass-mailing were randomised using a central block-randomisation process stratified according to screening centre, age and gender.
Allocation concealment (selection bias)		Low risk	Central randomisation process.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	Based on Cause of Death Registry.
Incomplete data (attribution bias)	Incidence/mortality	High risk	17.1 % of participants in the usual care group and 13.0 % in the intervention group refused further participation after 2009.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Parker 2002

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		High risk	Anxiety scores were measured in 100 test positive patients.
Allocation concealment (selection bias)		Low risk	See Scholefield 2012. Not relevant for this part of the study.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place.
Incomplete data (attribution bias)	Harms and burdens	Low risk	One person did not answer the questionnaire.

Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		High risk	No baseline measurement.

Pitkaniemi 2015

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	Randomisation through population registry.
Allocation concealment (selection bias)		Low risk	Central randomisation procedure.
Blinding (performance and detection bias)	Harms and burdens	Low risk	The study only reports on numbers needed to diagnose further, which does not occur in the control group.
Incomplete data (attribution bias)	Harms and burdens	Low risk	Subjects who died after the retrieving of the population sample but before or at the date of randomisation were excluded (94 in total; 49 invitees and 45 controls). Similarly excluded those who emigrated (in total 7; 4 invitees and 3 controls). Subjects who were diagnosed with CRC before or at the date of the randomisation were also excluded (1572; 817 invitees and 755 controls). Intention-to-treat analyses.
Selective reporting (reporting bias)	Harms and burdens	High risk	No data on other harms and burdens than number needed to go to further diagnostic work-up reported.
Other bias		Low risk	No other threats to validity detected.

Quintero 2012

Bias	Outcomes	Author's judgement	

Random sequence generation (selection bias)		Low risk	Subjects were identified through each Community Health Registry, sorted according to household, and stratified according to age (in 5-year age groups) and sex. Households were randomly assigned in a 1:1 ratio to undergo either one-time colonoscopy or biennial FIT.
Allocation concealment (selection bias)		Low risk	Randomization was performed before invitation with the use of a computer-generated allocation algorithm on the basis of a randomized-blocks method.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Harms and burdens	High risk	The participation rate is small in both groups (24.6 % for colonoscopy and 34.2 % for FIT), but the groups are similar. It is not described how information on harms and burdens were obtained.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant data were reported.
Other bias		Low risk	No other threats to validity detected.

Robinson 1999

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		Low risk	See Scholefield 2012.
Allocation concealment (selection bias)		Low risk	See Scholefield 2012.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Scholefield 2012.

	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	See Scholefield 2012.
	Harms and burdens	High risk	It is not described how information on harms and burdens were obtained.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant data were reported.
	Harms and burdens	Low risk	All relevant data were reported.
Other bias		Low risk	No other threats to validity detected.

Schoen 2000

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		High risk	All individuals at two screening centres in the period between May 30, 1996, and August 30, 1997, were recruited, of whom 97 % were participating in the PLCO trial.
Allocation concealment (selection bias)		High risk	For the PLCO participants, there were a central randomisation process. For the others, it i unknown.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Harms and burdens	High risk	Loss to answer questionnaire not reported.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.

Other bias		Low risk	No other threats to validity detected.

Schoen 2012

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Miller 2018.
Allocation concealment (selection bias)		Low risk	See Miller 2018.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	Death review group unaware of group allocation.
	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	Vital status was known for 99.9% of participants, and adherence with the annual study update questionnaire was 93.8%.
	Harms and burdens	High risk	It is not described how information on harms and burdens were obtained.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
	Harms and burdens	High risk	No reports of harms and burdens due to colonoscopy work-up.
Other bias		Low risk	No other threats to validity detected.

Scholefield 2002

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Scholefield 2012.
Allocation concealment (selection bias)		Low risk	See Scholefield 2012.

Blinding (performance and detection bias)	Incidence/mortality	Low risk	See Scholefield 2012.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	547 persons could not be traced or had emigrated.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Scholefield 2012

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	Central randomisation process by household. More than 50% of households were single persons.
Allocation concealment (selection bias)		Low risk	Central randomisation procedure.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	Study investigators who assessed cause of death and pathologists were unaware of group allocation.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	875 people could not be traced or had emigrated after randomisation and were excluded from analyses. Not stated how many people were lost to follow-up.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Segnan 2002

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Segnan 2011.
Allocation concealment (selection bias)		Low risk	See Segnan 2011.

	Incidence/mortality	Low risk	See Segnan 2011.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
	Incidence/mortality	Low risk	See Segnan 2011.
Incomplete data (attribution bias)	Harms and burdens	High risk	It is not described how information on harms and burdens were obtained.
	Incidence/mortality	Low risk	See Segnan 2011.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	See Segnan 2011.

Segnan 2011

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		Low risk	Computer-generated random number sequence.
Allocation concealment (selection bias)		Low risk	Allocation concealment was secured by using a computer-generated allocation algorithm.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	The independent investigators who assessed outcomes were blinded to group allocation.
Incomplete data (attribution bias)	Incidence/mortality	Low risk	280 (1.6%) individuals in the intervention group and 324 (1.9%) in the control group could not be traced.
Selective reporting (reporting bias)	Incidence/mortality	Low risk	All relevant outcomes were reported.

Other bias	Low risk	No other threats to validity detected.

Shaukat 2013

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	Weekly randomisation as participants were enrolled after stratification for age, sex and place of residence.
Allocation concealment (selection bias)		Low risk	Participants stratified and placed in groups of three who were subsequently randomised to one of six permutations which allocated the three participants to either of the three study groups.
Blinding (performance and detection bias)	Incidence/mortality	Low risk	The determination of all other causes of death was based on coded death certificates, which were coded by the study staff during the first 18 years and were subsequently obtained from the National Death Index (NDI; with the use of the NDI Plus service).
Incomplete data (attribution bias)	Incidence/mortality	High risk	Loss to follow-up not reported.
Selective reporting (reporting bias)	Incidence/mortality	High risk	Do not report on incidence.
Other bias		Low risk	No other threats to validity detected.

Wardle 2003

Bias	Outcomes	Author's judgement	Support for judgement
Random sequence generation (selection bias)		Low risk	See Atkin 2017.
Allocation concealment (selection bias)		Low risk	See Atkin 2017.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure

			not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Harms and burdens	Low risk	All groups are similar.
Selective reporting (reporting bias)	Harms and burdens	Low risk	All relevant outcomes were reported.
Other bias		Low risk	No other threats to validity detected.

Weissfeld 2005

Bias	**Outcomes**	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)		Low risk	See Miller 2018.
Allocation concealment (selection bias)		Low risk	See Miller 2018.
Blinding (performance and detection bias)	Harms and burdens	Low risk	None of the harms and burdens would have happened in the control group, due to the procedure not taking place. Blinding would not affect the reporting of these harms and burdens.
Incomplete data (attribution bias)	Harms and burdens	High risk	It is not described how information on harms and burdens were obtained.
Selective reporting (reporting bias)	Harms and burdens	High risk	No reports of harms and burdens due to colonoscopy work-up.
Other bias		Low risk	No other threats to validity detected.

Appendix 4: Supplementary tables and figures

Supplementary table 1a: No-screening vs annual gFOBT screening: Relative direct and indirect effect estimates for incidence and mortality

For relative and absolute NMA estimates, and evaluation of certainty, see Table 2b.

Outcome		RR	CI
Colorectal cancer incidence			
	Direct	0.81	0.67 to 0.88
	Indirect	1.09	0.47 to 1.60
Colorectal cancer mortality			
	Direct	0.68	0.54 to 0.85
	Indirect	0.77	0.51 to 1.16
All-cause mortality			
	Direct	1.00	0.97 to 1.03
	Indirect	1.02	0.96 to 1.08

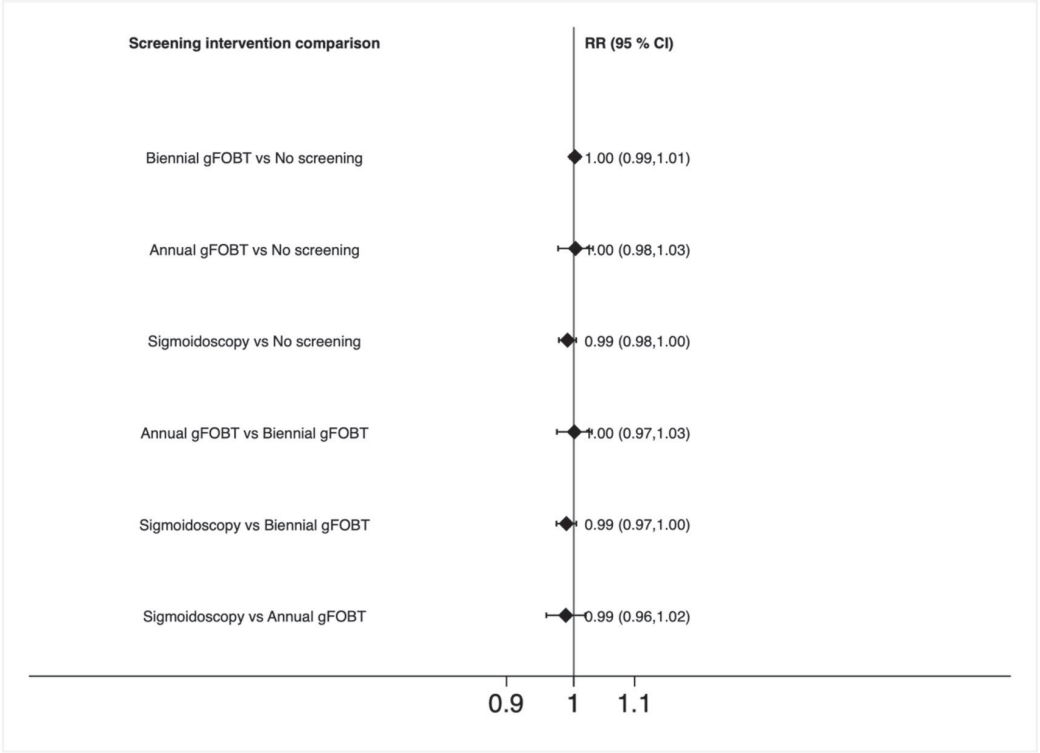
Supplementary table 1b: Biennial vs annual gFOBT screening: Relative and absolute direct and indirect effect estimates for incidence and mortality in a 15-year perspective

For relative and absolute NMA estimates, and evaluation of certainty, see Table 2c.

Outcome		**RR**	**CI**
Colorectal cancer incidence			
	Direct	0.96	0.79 to 1.06
	Indirect	0.72	0.49 to 1.06
Colorectal cancer mortality			
	Direct	0.82	0.64 to 1.04
	Indirect	0.72	0.48 to 2.02
All-cause mortality			
	Direct	1.01	0.97 to 1.04
	Indirect	0.99	0.93 to 1.04

Jodal HC, *et al. BMJ Open* 2019; 9:e032773. doi: 10.1136/bmjopen-2019-032773

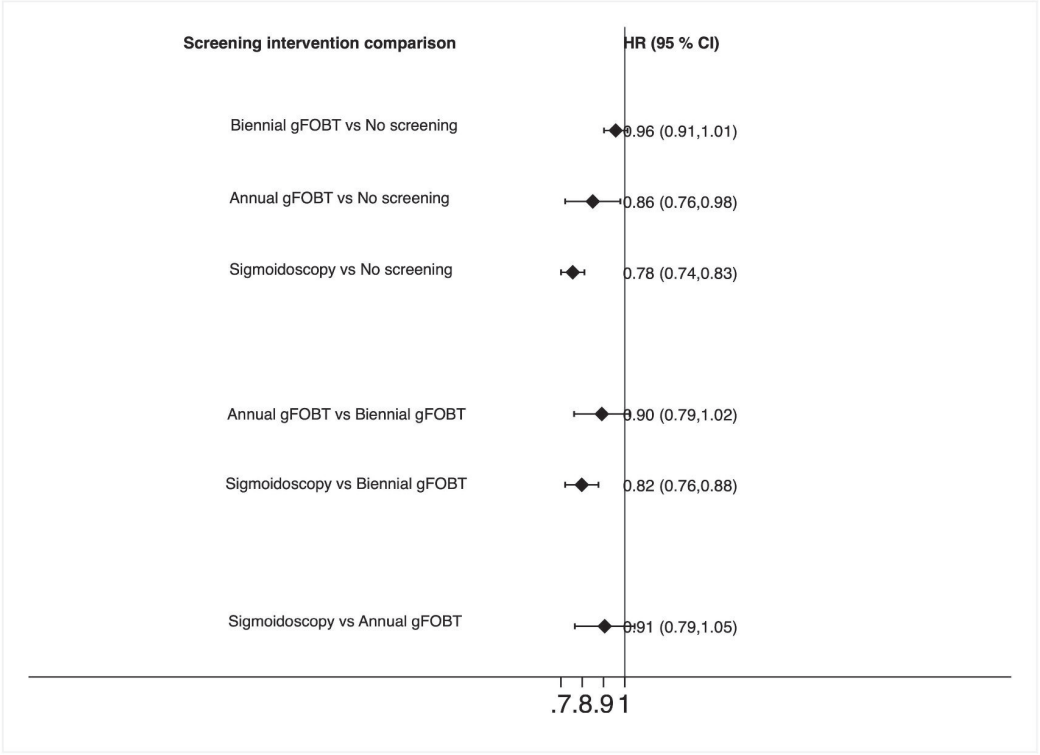
Supplementary figure 1: Effect of different screening interventions on all-cause mortality
Shown as relative risks with 95 % CIs.



Jodal HC, *et al. BMJ Open* 2019; 9:e032773. doi: 10.1136/bmjopen-2019-032773

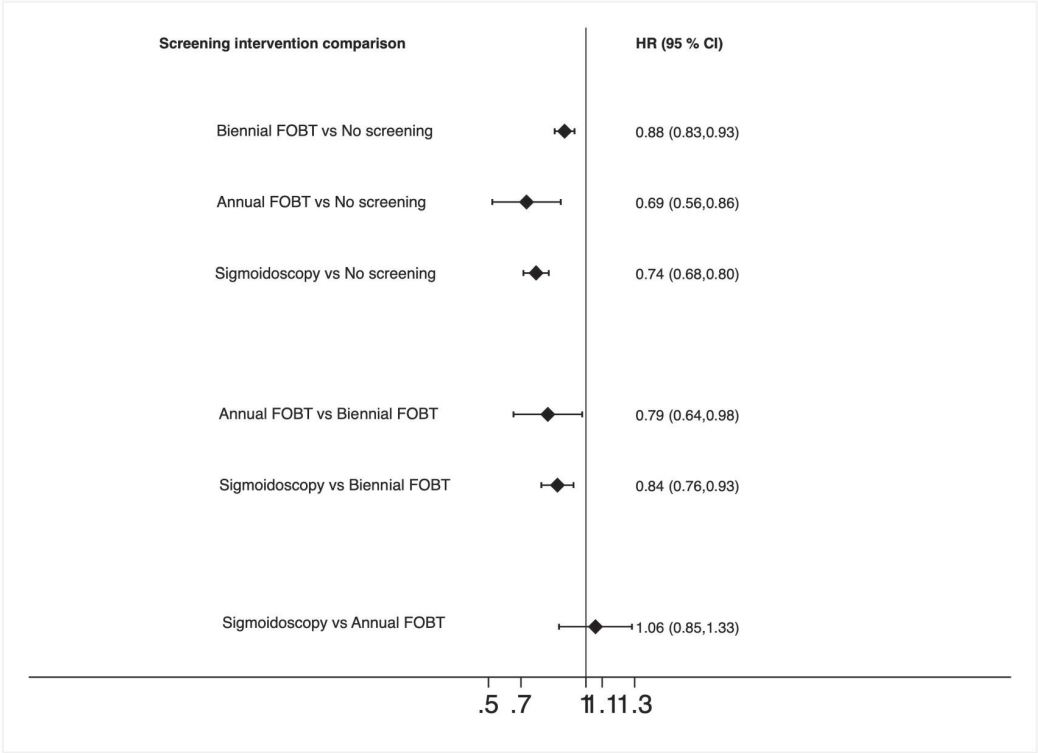
Supplementary figure 2: Effect of different screening interventions on colorectal cancer incidence

Shown as hazard ratios with 95 % CIs.



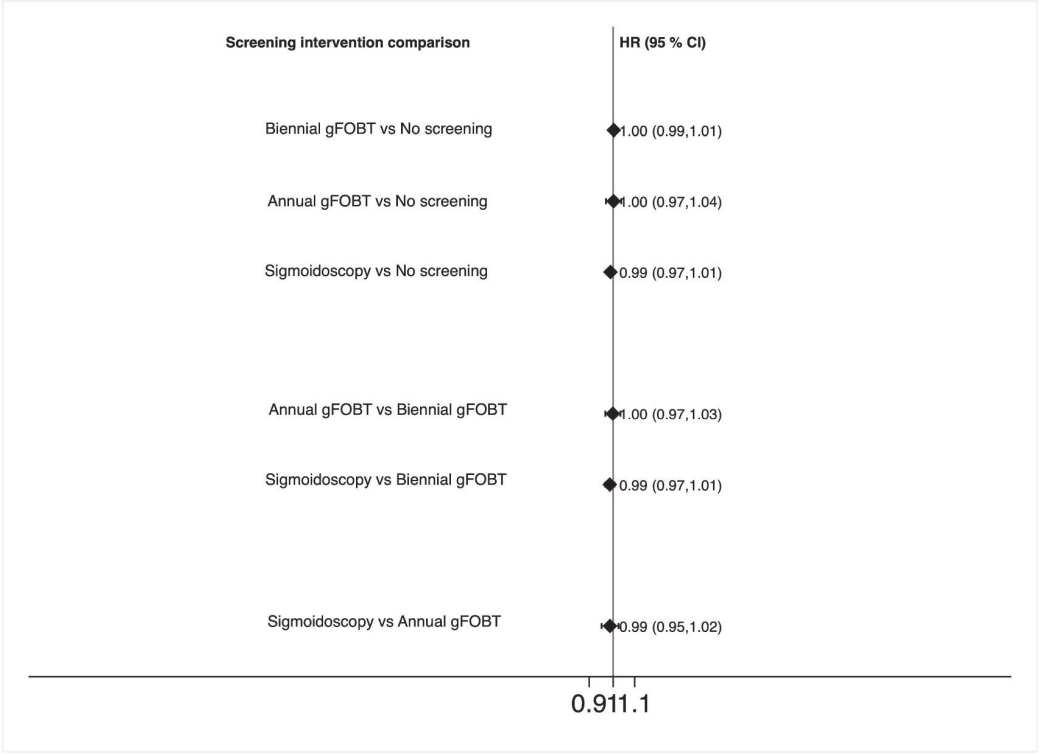
Supplementary figure 3: Effect of different screening interventions on colorectal cancer mortality

Shown as hazard ratios with 95 % CIs.

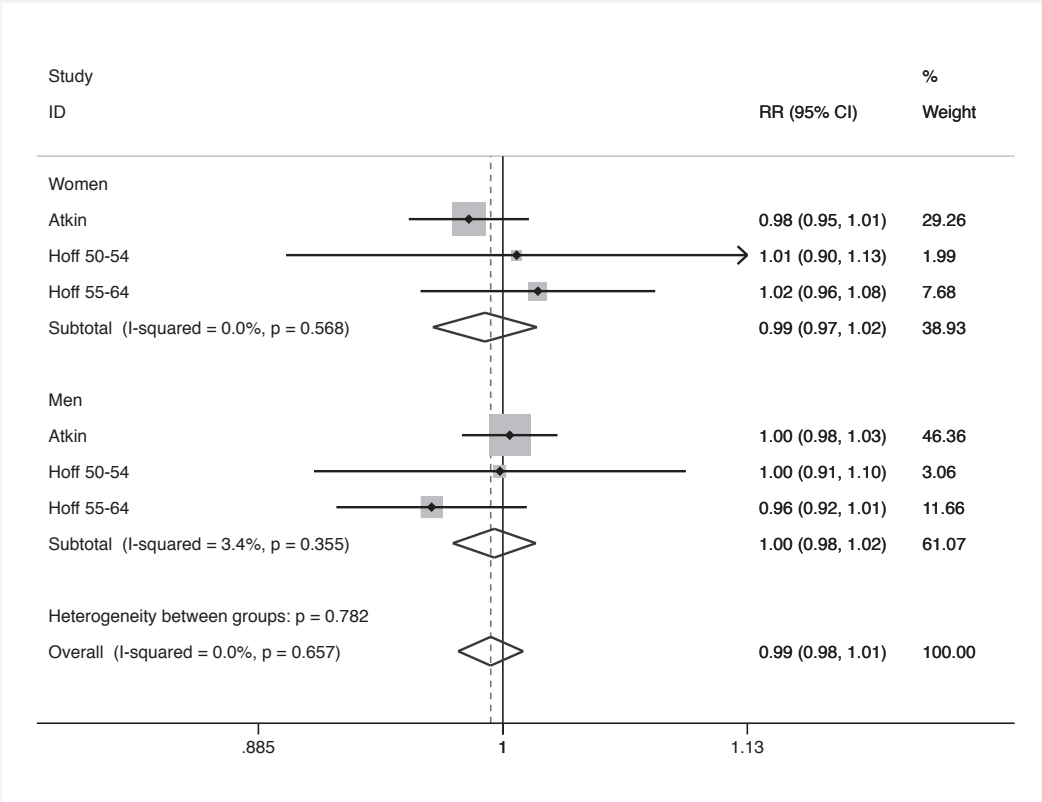


Jodal HC, *et al. BMJ Open* 2019; 9:e032773. doi: 10.1136/bmjopen-2019-032773

Supplementary figure 4: Effect of different screening interventions on all-cause mortality
Shown as hazard ratios with 95 % CIs.



Supplementary figure 5: Sex differences on all-cause mortality with sigmoidoscopy screening compared to no-screening



Supplementary table 2: Credibility of the subgroup difference of sex[61]

Criteria	**Judgment**
Is the subgroup variable a characteristic measured at baseline?	Yes.
Is the effect suggested by comparison within rather than between studies?	Yes.
Is the hypothesis specified a priori?	No.
Is the direction of subgroup effect specified a priori?	No.
Is it one of a small number of hypothesised effects tested?	Yes.
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes; colorectal cancer incidence: p=0.001 colorectal cancer mortality: p=0.015
Is the significant subgroup effect independent?	Not applicable.
Is the size of the subgroup effect large?	Yes; colorectal cancer incidence: - women: RR 0.86 (95 % CI 0.81-0.92) - men: RR 0.75 (95 % CI 0.71-0.79) colorectal cancer mortality: - women: RR 0.85 (95 % CI 0.71-0.96) - men: RR 0.67 (95 % CI 0.61-0.75)
Is the subgroup effect consistent across studies?	Yes, in three out of the four sigmoidoscopy trials included.
Is the subgroup effect consistent across closely related outcomes within study?	Yes, consistent across colorectal cancer incidence and colorectal cancer mortality.
Is there a biological rationale?	No convincing rationale.

Supplementary table 3a: Evidence profile of harms and burdens: No-screening vs sigmoidoscopy screening in a 15-year perspective

Outcome	Study results and measurements	Absolute effect estimates	Certainty in effect estimates	Plain text summary
Work-up procedure	Based on data from 128,203 patients in four studies. Follow-up: 10.5-17.1 years.	Among 100 screening attendees, 13 individuals (95 % CI 5 to 26) had a positive screening test, and thus required further work-up.	Moderate (serious indirectness)	Sigmoidoscopy screening probably leads to referral for work-up colonoscopy in five to 26 per 100 screened individuals.
Surveillance endoscopy	Based on data from 128,203 patients in four studies. Follow-up: 10.5-17.1 years	Among 100 screening attendees, four individuals (95 % CI three to five) had adenomas at work-up following the screening, which required further surveillance.	Low (serious risk of bias and serious indirectness)	Sigmoidoscopy screening may lead to surveillance colonoscopies in three to five per 100 screened individuals
Bleeding, up to one month after last procedure	Based on data from 118,292 patients in three studies. Follow-up: 10.5-17.1 years.	Among 10,000 screening attendees, three individuals (95 % CI one to six) had a bleed requiring hospitalisation, following the screening episode or subsequent work-up.	Moderate (serious risk of bias)	Sigmoidoscopy screening and subsequent work-up procedures may cause bleeding requiring hospitalisation in one to six per 10,000 screened individuals .
Perforation, up to one month after last procedure	Based on data from 128,203 patients in four studies. Follow-up: 10.5-17.1 years	Among 10,000 screening attendees, three individuals (95 % CI one to	Moderate (serious risk of bias)	Sigmoidoscopy screening and subsequent work-up procedures may cause

		four) had a perforation following diagnostic work-up after an initial positive screening test.		perforation of the colon or rectum in one to four per 10,000 screened individuals.
Death <30 days of procedure	Based on data from 40,674 patients in one study. Follow-up: 17.1 years.	Among 10,000 screening attendees, two individuals (95 % CI one to four) died the first 30 days after screening or subsequent work-up.	Moderate (serious risk of bias)	Sigmoidoscopy screening and subsequent work-up may cause death in one to four per 10,000 screened individuals.
Death <30 days of surgery	Based on data from 53,634 patients in two studies. Follow-up: 14.8-17.1 years.	Among 10,000 screening attendees, one individual (95 % zero to two) died the first 30 days following surgery, which was performed due to findings at screening or subsequent work-up.	Moderate (serious risk of bias)	Surgery due to a positive sigmoidoscopy screening may cause none to two deaths per 10,000 screened individuals.
Major complications	Based on data from 53,634 patients in two studies. Follow-up: 14.8-17.1 years.	Among 10,000 screening attendees, one individual (95 % CI zero to two) experienced major complications.	Moderate (serious risk of bias)	Sigmoidoscopy screening and subsequent work-up may cause none to two major complications (such as heart attack) per 10,000 screened individuals.
Miscellaneous adverse events	Based on data from 63,545 patients in three studies. Follow-up: 10.5-17.1 years.	Among 10,000 screening attendees, 68 individuals (95 % CI 41-90) experienced	Moderate (serious risk of bias)	Sigmoidoscopy screening and subsequent work-up may cause 41 to 90 miscellaneous

		miscellaneous adverse events.		adverse events (such as syncope) per 10,000 screened individuals.
Pain	Based on data from 54,842 patients in four studies. Follow-up: 10.5-17.1 years.	Among 100 screening attendees, 16 individuals (95 % 10-22) reported moderate-severe pain during the procedure.	Low (serious risk of bias and serious inconsistency)	Sigmoidoscopy screening may cause moderate to severe pain during the screening procedure in 10 to 22 per 100 screened individuals.

Supplementary table 3b: Evidence profile of harms and burdens: No-screening vs gFOBT screening per two to five screening rounds

Outcome	Study results and measurements	Absolute effect estimates	Certainty in effect estimates	Plain text summary
Work-up procedure	Based on data from 89,426 patients in three studies. Follow-up: 15.5-19.5 years.	Among 100 screening attendees, six individuals (95 % CI four to nine) had a positive screening test, and thus required further work-up.	Moderate (serious indirectness)	gFOBT screening probably leads to referral for work-up colonoscopy in four to nine out of 100 screened individuals after two to five screening rounds.
Surveillance endoscopy	Based on data from 89,426 patients in three studies. Follow-up: 15.5-19.5 years.	Among 100 screening attendees, one individual (95 % CI one to two) had adenomas at work-up following the screening, which required further surveillance.	Low (very serious indirectness)	gFOBT screening may lead to surveillance colonoscopies in one to two per 100 screened individuals after two to five screening rounds.
Bleeding, up to one month after procedure	Based on data from 68,754 patients in two studies. Follow-up: 15.5-19.5 years.	Among 10,000 screening attendees, no individuals (95 % CI zero to one) had a bleed requiring hospitalisation, following the screening episode or subsequent work-up.	Low (serious risk of bias and serious indirectness)	gFOBT screening and subsequent work-up procedures may cause bleeding requiring hospitalisation in none to one per 10,000 screened individuals after two to five screening rounds.

Perforation, up to one month after last procedure	Based on data from 68,754 patients in two studies. Follow-up: 15.5-19.5 years.	Among 10,000 screening attendees, one individual (95 % CI one to two) had a perforation following diagnostic work-up after an initial positive screening test.	Low (serious risk of bias and serious indirectness)	gFOBT screening and subsequent work-up procedures may cause perforation of the colon or rectum in one to two per 10,000 screened individuals after two to five screening rounds.
Death <30 days of procedure	Based on data from 68,754 patients in two studies. Follow-up: 15.5-19.5 years.	No screening attendees (95 % CI NA) died the first 30 days after screening or subsequent work-up.	Low (serious risk of bias and serious indirectness)	gFOBT screening and subsequent work-up procedures may not cause death after two to five screening rounds.
Death <30 days of surgery	Based on data from 68,754 patients in two studies. Follow-up: 15.5-19.5 years.	Among 10,000 screening attendees, one person (95 % CI zero to one) died the first 30 days following surgery, which was performed due to findings at screening or subsequent work-up.	Low (serious risk of bias and serious indirectness)	Surgery due to a positive gFOBT screening result may cause death in none to one per 10,000 screened individuals after two to five screening rounds.
Major complications	Based on data from 68,754 patients in two studies. Follow-up: 15.5-19.5 years.	No screening attendees (95 % CI NA) experienced major complications.	Low (serious risk of bias and serious indirectness)	gFOBT screening and subsequent work-up may not cause any major complications after two to

				five screening rounds.
Miscellaneous adverse events	Based on data from 68,754 patients in two studies. Follow-up: 15.5-19.5 years.	Among 10,000 screening attendees, one individual (95 % one to two) experienced miscellaneous adverse events.	Low (serious risk of bias and serious indirectness)	gFOBT screening and subsequent work-up may cause miscellaneous adverse events (such as syncope) in one to two per 10,000 screened individuals after two to five screening rounds.

Supplementary table 3c: Evidence profile of harms and burdens: No-screening vs FIT screening per screening test

Outcome	Study results and measurements	Absolute effect estimates	Certainty in effect estimates	Plain text summary
Work-up procedure	Based on data from 10,611 patients in one study. Follow-up: Baseline.	Among 100 screening attendees with one test, seven individuals (95 % CI seven to eight) had a positive screening test, and thus required further work-up.	Moderate (serious indirectness)	FIT screening probably leads to referral for work-up colonoscopy in seven to eight out of 100 screening tests performed.
Surveillance endoscopy	Based on data from 10,611 patients in one study. Follow-up: Baseline.	Among 100 screening attendees with one test, two individuals (95 % CI two to three) had adenomas at work-up following the screening, which required further surveillance.	Moderate (serious indirectness)	FIT screening probably leads to surveillance colonoscopies in two to three out of 100 screening tests performed.
Bleeding, up to one month after procedure	Based on data from 10,611 patients in one study. Follow-up: Baseline.	Among 10,000 screening attendees with one test, eight individuals (95 % CI three to 14) had a bleed requiring hospitalisation, following the screening episode or subsequent work-up.	Low (serious risk of bias and serious indirectness)	FIT screening and subsequent work-up procedures may cause bleeding requiring hospitalisation in three to 14 per 10,000 screening tests performed.
Perforation, up to one month after procedure	Based on data from 10,611 patients in one study. Follow-up: Baseline.	Among 10,000 screening attendees with one test, no	Low (serious risk of bias and serious indirectness)	FIT screening and subsequent work-up procedures may

		persons (95 % CI NA) had a perforation following diagnostic work-up after an initial positive screening test.		not cause any deaths.
Major complications	Based on data from 10,611 patients in one study. Follow-up: Baseline.	Among 10,000 screening attendees with one test, two individuals (95 % CI zero to seven) experienced major complications.	Low (serious risk of bias and serious indirectness)	FIT screening and subsequent work-up may cause major complications (such as heart attack) in none to seven per 10,000 screening tests performed.

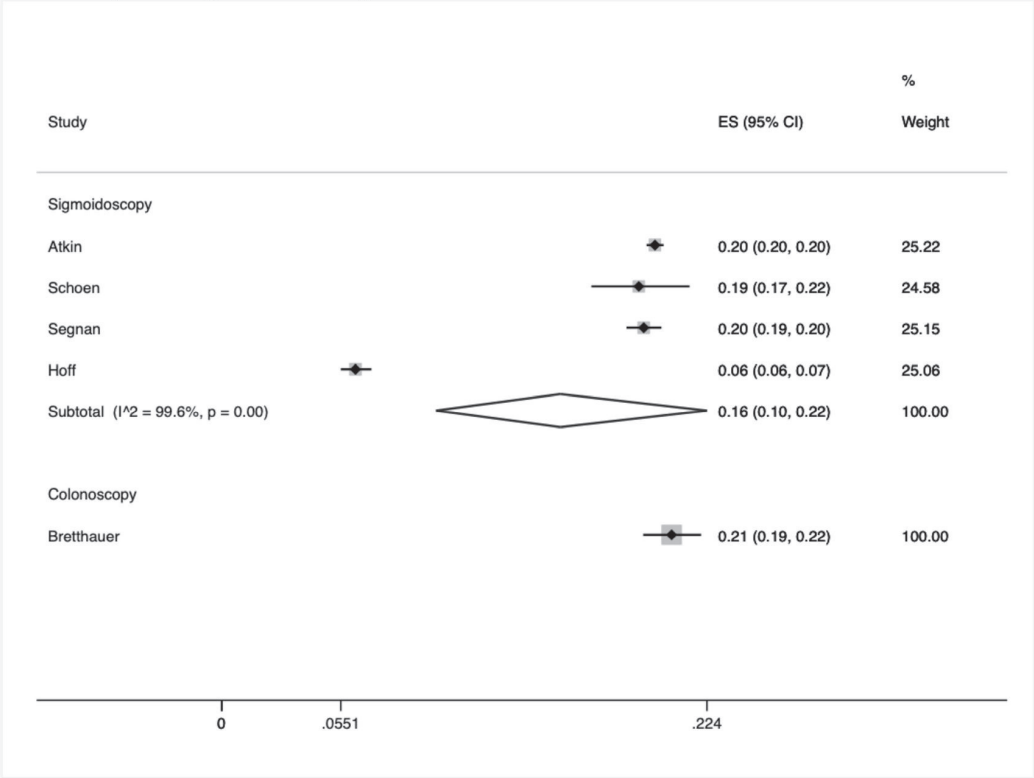
Supplementary table 3d: Evidence profile of harms and burdens: No-screening vs colonoscopy screening in a 15-year perspective

Outcome	Study results and measurements	Absolute effect estimates	Certainty in effect estimates	Plain text summary
Surveillance endoscopy	Based on data from 17,633 patients in two studies. Follow-up: Baseline.	Among 100 screening attendees, ten persons (95 % CI ten to 11) had adenomas at work-up following the screening, which required further surveillance.	Moderate (serious indirectness)	Colonoscopy screening probably leads to surveillance colonoscopies in ten to 11 out of 100 individuals screened.
Bleeding, up to one month after procedure	Based on data from 17,633 patients in two studies. Follow-up: Baseline.	Among 10,000 screening attendees, 17 persons (95 % CI 12 to 23) had a bleed requiring hospitalisation, following the screening episode.	Moderate (serious risk of bias)	Colonoscopy screening and subsequent work-up procedures may cause bleeding requiring hospitalisation in 12 to 23 per 10,000 screened individuals.
Perforation, up to one month after procedure)	Based on data from 17,633 patients in two studies. Follow-up: Baseline.	Among 10,000 screening attendees, one individual (95 % CI zero to three) had a perforation following diagnostic work-up after an initial positive screening test.	Moderate (serious risk of bias)	Colonoscopy screening and subsequent work-up procedures may cause perforation of the colon or rectum in none to three per 10,000 individuals screened.
Death <30 days of procedure	Based on data from 12,574 patients in one study. Follow-up: Baseline.	Among 10,000 screening attendees, no individuals (95 % CI NA) died the first 30 days after screening or	Moderate (serious risk of bias)	Colonoscopy screening and subsequent work-up procedures may not cause any deaths.

		subsequent work-up.		
Major complications	Based on data from 17,633 patients in two studies. Follow-up: Baseline.	Among 10,000 screening attendees, two individuals (95 % CI zero to five) experienced major complications.	Moderate (serious risk of bias)	Colonoscopy screening and subsequent work-up may cause major complications (such as heart attack) in none to five per 10,000 screened individuals.
Miscellaneous adverse events	Based on data from 12,574 patients in one study. Follow-up: Baseline.	Among 10,000 screening attendees, 41 persons (95 % CI 32 to 50) experienced miscellaneous adverse events.	Moderate (serious risk of bias)	Colonoscopy screening and subsequent work-up may cause miscellaneous adverse events (such as syncope) in 32 to 50 per 10,000 screened individuals.
Pain	Based on data from 3601 patients in one study. Follow-up: Baseline.	Among 100 screening attendees, 21 persons (95 % 19 to 22) reported moderate-severe pain during the procedure, independent of use of anaesthesia and air or CO2 insufflation.	High	Colonoscopy screening cause moderate to severe pain during the screening procedure in 19 to 22 out of 100 screened individuals.

Supplementary figure 6: Risk of experiencing moderate-severe pain during screening procedure

Shown as percentage of screening attenders with 95 % CIs.



III

Long-Term Colorectal Cancer Incidence and Mortality after Adenoma Removal in Women and Men

Running title: Colorectal Cancer after Adenoma Removal

Henriette C. Jodal, MD[1], Dagmar Klotz, MD[1,2], Magnhild Herfindal[1], Ishita Barua, MD[1], Petter Tag, MD[3], Lise M. Helsingen, MD[1], Erle Refsum, MD PhD[1], Øyvind Holme, MD PhD[1,4], Hans-Olov Adami, MD PhD[1,5], Michael Bretthauer, MD PhD[1], Mette Kalager, MD PhD[1,6], Magnus Løberg, MD PhD[1]

[1]Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, and Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway

[2]Department of Pathology, Oslo University Hospital, Oslo, Norway

[3]Department of Medicine, Nordland Hospital Bodø, Norway

[4]Department of Medicine, Sørlandet Hospital Kristiansand, Norway

[5]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

[6]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA

Abbreviations: HR: hazard ratio; CI: confidence interval; IQR: inter-quartile range; SMR: standardized incidence-based mortality ratio; SIR: standardized incidence ratio

Correspondence: Henriette C. Jodal MD, Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, Oslo, Norway. E-mail: h.c.jodal@medisin.uio.no Telephone: +47 410 86 420

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Summary

Background

Women and men with adenomas are considered at increased colorectal cancer risk and recommended colonoscopy surveillance. However, the long-term cancer risk remains unknown.

Aims

We investigated colorectal cancer incidence and mortality after adenoma removal in women and men.

Methods

We identified all individuals who had adenomas removed in Norway from 1993-2007, with follow-up through 2018. We calculated standardized incidence (SIR) and incidence-based mortality ratios (SMR) for colorectal cancer in women and men with 95% confidence intervals (CI) using the female and male population for comparison. We defined high-risk adenomas as ≥2 adenomas, villous component, or high-grade dysplasia.

Results

The cohort comprised 40,293 individuals. During median follow-up of 13.0 years, 1,079 women (5.5%) and 866 men (4.2%) developed colorectal cancer; 328 women (1.7%) and 275 men (1.3%) died of colorectal cancer. Colorectal cancer incidence was more increased in women (SIR 1.64,95%CI 1.54-1.74) than in men (SIR 1.12, 5%CI 1.05-1.19). Colorectal cancer mortality was increased in women (SMR 1.13,95%CI 1.02-1.26) and reduced in men (SMR 0.79, 95%CI 0.71-0.89). Women with high-risk adenomas had increased risk of colorectal cancer death (SMR 1.37,95%CI 1.19-1.57), women with low-risk adenomas (SMR 0.90,95%CI 0.76-1.07) and men with high-risk adenomas had similar risk (SMR 0.89,95%CI

0.76-1.04), while men with low-risk adenomas had reduced risk (SMR 0.70,95%CI 0.59-0.84).

Conclusions

After adenoma removal, women had increased risk of colorectal cancer death, while men had reduced risk, compared to the general female and male populations. Women do not benefit from intensive surveillance after adenoma removal.

Keywords

colorectal cancer, adenoma, screening, surveillance

Introduction

Colorectal cancer is the third most common malignancy worldwide, and the second most common cause of cancer-related deaths.[1] Screening programs with faecal occult blood tests (FOBT), sigmoidoscopy or colonoscopy have been introduced in many countries.[2] The aim of screening is to reduce cancer incidence through removal of adenomas, and reduce cancer mortality through incidence reduction and early detection of cancer.[3]

Individuals who have had adenomas removed are considered at increased risk of developing new adenomas and colorectal cancer in the future, and are therefore recommended endoscopic surveillance. As adenomas are found in more than 20% of women and 30% of men during screening,[4,5] and screening activity is increasing, the number of individuals recommended surveillance after adenoma removal is growing rapidly and might limit the availability of colonoscopy resources for diagnostic and therapeutic purposes.[6]

We have previously shown that individuals who have had low-risk adenomas removed have a lower risk of colorectal cancer mortality than the general population,[7,8] a finding later confirmed by others.[9-12] Although individuals who have had high-risk adenomas removed have a higher risk of colorectal cancer death in most studies,[7,8,11,12] the magnitude and duration of excess risk is uncertain due to low precision and usually less than 10 years of follow-up.[11-15] Nevertheless, individuals are currently recommended frequent surveillance colonoscopy after adenoma removal, typically every 3, 5, or 10 years depending on adenoma characteristics.[16-18] These recommendations are based on scarce evidence.

There is emerging evidence that endoscopic screening may convey less benefit in women than in men.[19-21] Thus, it is imminent to investigate if women and men have different risks for

colorectal cancer incidence and mortality after adenoma removal, and consider sex-specific surveillance.

We here update our previous report on colorectal cancer incidence and mortality after removal of low- and high-risk adenomas in a large population-based cohort,[7] now with 13.0 years of follow-up and sex-stratified analysis.

Materials and Methods

Data sources

Norway has a public, single-payer healthcare system with universal coverage. All residents are assigned an individually unique national registration number linked to information on sex and date of birth, through which residents can be identified in national registries and hospital databases. All residents are assigned to a general practitioner, and all referrals to specialized healthcare go through the general practitioner. Both the general practitioner and a gastroenterologist evaluate the clinical need of an endoscopic procedure before it is performed.

During the study period, no colorectal cancer screening program existed in Norway. Thus, individuals who had adenomas removed were referred to endoscopy due to symptoms. However, between 1999 and 2001, 2,208 individuals with adenoma were identified in a regional randomized sigmoidoscopy screening trial,[22] and these individuals are not excluded from this adenoma cohort.

The Cancer Registry of Norway contains data on individuals with cancer. Because reporting of all cancer cases is mandatory in Norway, registration is close to 100% complete.[23] Adenomas were similarly registered in the Cancer Registry between 1993 and 2007. The

Registry classifies all cancers and adenomas according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3). All adenomas reported to the Cancer Registry more than four months apart are recorded as separate occurrences.[7] As in our previous report, we pooled all adenomas within the same occurrence and classified the individual according to the most severe characteristic. The number of adenomas removed is recorded as single or multiple, and the size of the adenomas is not registered in the Cancer Registry.[7]

Before 2013, Norwegian guidelines recommended colonoscopy surveillance 10 years after adenoma removal for patients younger than 75 years with advanced adenomas (defined as high-grade dysplasia, villous growth pattern, or diameter ≥10 mm) and after 5 years for those with three or more adenomas.[24] Surveillance was not recommended for patients with low-risk adenomas nor for patients older than 74 years of age. In 2013, European Society of Gastrointestinal Endoscopy (ESGE) guidelines were implemented.[25]

Study design

From the Cancer Registry, we retrieved information on all individuals aged 40 years and older who had adenomas removed between 1993 and 2007, including dates of adenoma removal, colorectal cancer diagnosis, emigration, and death, until end of follow-up on 31st December 2018, and cause of death if cancer related. We excluded individuals with previous colorectal cancer, and individuals with familial adenomatous polyposis (through linkage with the Norwegian Polyposis Registry). Individuals were identified by topographical ICD-O-3 codes 180, 182 through 189, 199, or 209, combined with morphological ICD-O-3 codes 8140, 8210, 8211, 8261, or 8263. Adenoma location was defined as distal (rectum or sigmoid colon) or proximal (proximal to the sigmoid colon), multiple (distal and proximal), or unspecified (not registered). As previously reported, we classified high-risk adenomas as

adenomas with high-grade dysplasia, and/or a (tubulo-)villous growth pattern, and/or multiple adenomas (modified high-risk criteria),[7] which slightly differs from the established ESGE high-risk criteria (high-grade dysplasia, and/or (tubulo-)villous growth pattern, and/or ≥3 adenomas, and/or size ≥10 mm).[25]

We retrieved information on colorectal cancer cases and deaths in the general population from the Cancer Registry, and information on the population from Statistics Norway. The general population was stratified by age, sex, and calendar year of diagnosis. The matched general population was colorectal cancer-free until the year of first adenoma removal, similar to the study population who was excluded if they had a previous colorectal cancer. We compared observed colorectal cancer incidence and mortality in the adenoma cohort with rates in the general population.

Colorectal cancer mortality was our primary endpoint, and colorectal cancer incidence our secondary endpoint.

Medical chart review

To validate the accuracy of adenoma information and classification, we performed a manual medical chart review including original pathology and endoscopy reports. A random subcohort of 1,100 individuals were selected from the adenoma cohort,[7] of which 948 patient charts were obtained (Figure S1). Detailed information of the individuals' lower endoscopies, colectomies, and pathology reports was registered in a structured database.

Ethics and approvals

The study was approved by the Norwegian National Research Ethics Committee (2014/2352), which waived informed consent for patients included in the study due to its

registry-based design. All living individuals sampled for the manual chart review were provided with written information about the study and could opt out.

Statistical analyses

Analyses were performed for women and men separately. We calculated person-years at risk from date of adenoma removal until colorectal cancer diagnosis and until colorectal cancer death. All time-to-event data were censored at time of emigration, death, or end of follow-up (31st December 2018). For individuals who had adenomas removed on more than one occasion, person-years at risk were calculated separately following each adenoma removal. Person-years at risk were stratified according to sex, 5-year age group, calendar year and year of first adenoma removal. We calculated person-years at risk until colorectal cancer death for the general population in Norway. The number of events and person-years was used to calculate overall and adenoma location-specific incidence-based colorectal cancer mortality, as in our previous report.[8]

We calculated standardized incidence ratios (SIR) and standardized incidence-based mortality ratios (SMR) by dividing observed colorectal cancer cases and deaths among women and men in the cohort by the expected number of colorectal cancer cases and deaths that would have occurred if the cohort had had the same rate as the female and male background population. The rates of colorectal cancer diagnosis and death were derived as the number of colorectal cancer cases and deaths per 100,000 person-years at risk over the years of follow-up. We calculated 95% confidence intervals (CI) under the assumption that occurrence of events followed a Poisson distribution. We calculated SIR and SMR stratified by sex, age group, calendar period, and adenoma location and characteristics. We constructed cumulative curves for colorectal cancer mortality among women and men considered at low-

risk and high-risk after the initial adenoma removal, and we treated death from other causes as a competing risk. Cumulative curves were compared using Gray's test.[26]

We used Cox proportional hazard models stratified by sex, to estimate hazard ratios (HR) with 95% CI in order to separate out the effects of age, number of adenoma occurrences, adenoma location, number of adenomas, grade of dysplasia, growth pattern, and period of adenoma removal. We fitted multivariable models using stepwise regression with forward selection for inclusion of variables. The same model was used for women and for men.

Due to a higher proportion of women compared to men aged 80 years or older at first adenoma removal, we performed sensitivity analyses excluding these individuals. We also performed sensitivity analysis stratified on period of first adenoma removal (1993-1999 and 2000-2007), as clinical practice has evolved during the period of the study. As current guidelines recommend surveillance at the latest 10 years after adenoma removal,[16,18,27] we performed sensitivity analyses restricting to 10 years of follow-up. We also censored our follow-up at the next adenoma removal, to account for surveillance. All tests were two-sided, and P values less than 0.05 were considered statistically significant. Stata software version 16.1 (StataCorp, College Station, TX, USA) was used for analyses.

Results

Characteristics of the adenoma cohort

The adenoma cohort comprised 40,293 individuals, where 2,208 (5.5%) were identified at screening,[22] and the rest due to symptoms. Of these, 19,725 were women (49.0%) and 20,568 men (51.0%) (Table 1). A total of 45,340 adenoma removals were recorded, 22,017 in women (48.6%) and 23,323 in men (51.4%). The total follow-up time was 492,736 person-years (median 13.0 years, inter-quartile range (IQR) 7.3-17.0 years). A total of 26,461

individuals were alive and followed for 10 years or more. Median age at first adenoma, colorectal cancer diagnosis and colorectal cancer death was respectively 67.0, 79.9, and 80.2 years for women, and 65.4, 77.5, and 77.8 years for men. Table 1 displays individual characteristics and characteristics of removed adenomas in women and men.

Chart review study

Among the 948 individuals in the sample, 488 were women (51.5%) and 460 men (48.5%) (Table S1). Among the women, 230 (78.8%) out of 292 low-risk adenomas (sensitivity 84%, positive predictive value (PPV) 79%) and 208 (82.2%) out of 253 high-risk adenomas (sensitivity 77%, PPV 82%) were similarly classified using the modified high-risk criteria based on Cancer Registry data, where information on adenoma size and number was missing, compared to the ESGE criteria (Table S2). Among the men, 225 (79.2%) out of 284 low-risk adenomas (sensitivity 83%, PPV 79%) and 188 (80.3%) out of 234 high-risk adenomas (sensitivity 76%, PPV 80%) were similarly classified in the Cancer Registry (Table S2). Thus, the accuracy of the modified criteria was 80% for both women and men. Excluding the misclassified adenomas from the sample did not significantly change the distribution of individual and adenoma characteristics in the sample.

In the sample, 80% had a colonoscopy at their first adenoma removal, and there was no difference between women and men. The remaining 20% had a sigmoidoscopy, rectoscopy or colectomy.

Colorectal cancer incidence

A total of 1,945 individuals in the adenoma cohort (4.8%, 402 per 100,000 person-years) developed colorectal cancer during follow-up; 1,079 women (5.5%, 440 per 100,000 person-years) and 866 men (4.2%, 364 per 100,000 person-years) (Figure 1, Table S3). The absolute

risk of developing colorectal cancer in the general population was 269 per 100,000 person-years for women, and 325 per 100,000 person-years for men. Colorectal cancer incidence was more increased in women who had adenomas removed (SIR 1.64, 95% CI 1.54-1.74, 171 more cases per 100,000 person-years) than in men (SIR 1.12, 95% CI 1.05-1.19, 39 more cases per 100,000 person-years), as compared to women and men in the general population.

Women had a 2-fold increased colorectal cancer incidence after high-risk adenoma removal (SIR 1.99, 95% CI 1.84-2.15, 282 more cases per 100,000 person-years) compared to the female population, while the increase was less among women with low-risk adenomas (SIR 1.32, 95% CI 1.20-1.45, 81 more cases per 100,000 person-years).

Men also had increased colorectal cancer incidence after high-risk adenoma removal (SIR 1.36, 95% CI 1.25-1.49, 128 more cases per 100,000 person-years) compared to the male population, but reduced incidence after removal of low-risk adenomas (SIR 0.88, 95% CI 0.79-0.98, 36 fewer cases per 100,000 person-years).

Cumulative colorectal cancer incidence was significantly different between individuals after removal of low-risk compared to high-risk adenomas for both women and men (Gray's test P value<0.001) (Figure S2).

Colorectal cancer mortality

During follow-up, 603 individuals (1.5%, 122 per 100,000 person-years) died from colorectal cancer; 328 women (1.7%, 131 per 100,000 person-years) and 275 men (1.3%, 113 per 100,000 person-years) (Figure 1, 2, Table S4). The absolute risk of colorectal cancer death in the general population was 116 per 100,000 person-years for women, and 143 per 100,000 person-years for men. Compared to the general population, colorectal cancer mortality was increased for women after adenoma removal (SMR 1.13, 95% CI 1.02-1.26, 15 more deaths

per 100,000 person-years), and reduced for men (SMR 0.79, 95% CI 0.71-0.89, 29 fewer deaths per 100,000 person-years).

Women had higher colorectal cancer mortality than the female population after removal of high-risk adenomas (SMR 1.37, 95% CI 1.19-1.57, 47 more deaths per 100,000 person-years) (Figure 1, Table S4), while there was no difference after removal of low-risk adenomas (SMR 0.90, 95% CI 0.76-1.07, 10 fewer deaths per 100,000 person-years).

Men had similar colorectal cancer mortality to the male population after removal of high-risk adenomas (SMR 0.89, 95% CI 0.76-1.04, 18 fewer deaths per 100,000 person-years) (Figure 1, Table S4), while the mortality was reduced after removal of low-risk adenomas (SMR 0.70, 95% CI 0.59-0.84, 39 fewer deaths per 100,000 person-years).

Cumulative colorectal cancer mortality was significantly different between individuals after removal of low-risk and high-risk adenomas for both women and men (Gray's test P value<0.001) (Figure 3).

The risk of proximal colon cancer mortality was increased after a proximal adenoma removal for women (SMR 1.51, 95% CI 1.07-2.14), but not for men (SMR 1.29, 95% CI 0.89-1.89) (Table S5).

Results from univariable and multivariable analyses of colorectal cancer mortality comparing women and men in the adenoma cohort are shown in Table 2. In multivariable analysis, colorectal cancer mortality after adenoma removal increased with age at first adenoma removal, multiple or unspecified adenoma locations (women: HR 1.51, 95% CI 1.10-1.81; men: HR 1.58, 95% CI 1.22-2.06), multiple simultaneous adenomas (women: HR 1.41, 95% CI 1.10-1.81; men: HR 0.87, 95% CI 0.66-1.15), villous or tubulovillous growth pattern (women: HR 1.52, 95% CI 1.21-1.91; men: HR 1.55, 95% CI 1.20-2.00), and high-grade

dysplasia (women: HR 1.58, 95% CI 1.10-2.25; men: HR 1.38, 95% CI 0.92-2.08). Colorectal cancer mortality was lower among those who had their first adenoma removed in years 2000-2007 (women: HR 0.77, 95% CI 0.61-0.97; men: HR 0.70, 95% CI 0.55-0.90), than those who had their first adenoma removed in 1993-1999.

Sensitivity analysis

In sensitivity analyses where we excluded individuals aged 80 years or older at first adenoma, or stratified by the period of first adenoma removal (1993-1999 or 2000-2007), the results did not change (data not shown). When we restricted the analyses to 10 years of follow-up, results were similar (Table S6). Censoring follow-up at the next adenoma removal did not affect the results (data not shown).

Discussion

Our study revealed that compared to the general female and male population, both women and men have increased colorectal cancer incidence after adenoma removal, while colorectal cancer mortality is increased for women, but reduced for men. Women had 37% increased colorectal cancer mortality after removal of high-risk adenomas (47 more per 100,000 person-years) compared to the female population. Women who had low-risk adenomas removed, and men who had high-risk adenomas removed, had similar mortality as the female and male population respectively. Men had 30% reduced colorectal cancer mortality after removal of low-risk adenomas (39 fewer per 100,000 person-years) compared to the male population.

Colorectal cancer incidence and mortality is higher in the general male population than in the female. After adenoma removal, colorectal cancer mortality was 131 per 100,000 person-years (95% CI 118-147 per 100,000 person-years) in women and 113 per 100,000 person-

years (95% CI 101-128 per 100,000 person-years) in men. As previously suggested,[20] this might indicate that colorectal adenomas are the most robust cancer risk predictors, and that adenoma removal can reduce the risk to a certain level, irrespective of other risk factors, but not below that level. In a Swedish study, the incidence and mortality of colorectal cancer after adenoma removal was similar to what is observed here, while the risk in the general population was much lower, in line with national cancer statistics between Norway and Sweden.[12] Consequently, a larger excess risk was seen in the Swedish cohort than in our study.[8] This observation is in line with our observed difference between women and men, and the ability of adenomas to predict risk irrespective of background risk in the population.

We found that both women and men who had low-risk adenomas removed had lower colorectal cancer mortality than the general population, a choice of comparison group endorsed by the World Endoscopy Organization.[28] This is different from previous studies, where colorectal cancer mortality was similar after removal of low-risk adenomas, compared to individuals who are adenoma-free at screening.[9,10,14,29] The difference in comparison group likely explain the differing results: the comparison group of the general population resembles the control group in a screening trial, i.e. a mixture of individuals with and without adenomas, while the comparison group of the adenoma-free resembles screening compliers without findings at screening colonoscopy, a group recognized to have a minimal risk of colorectal cancer.

Strengths of our study include the large size, population-based design, and complete long-term follow-up. A limitation is the lack of detailed information about the number and size of removed adenomas. However, we performed a chart review of a random sample of the adenoma cohort which showed adequate consistency of the registry data applied. As in our previous report, the observed misclassification of some individuals may have led to

overestimation of the true risk for individuals both after removal of low- and high-risk adenomas:[7] The gross majority of those who changed risk group after chart review, did so because of adenoma size larger than 10 mm. These individuals, whose adenomas harbour only a single high-risk characteristic, probably increase the observed risk after removal of low-risk adenomas. Had they correctly been included among those who had high-risk adenomas removed, the risk after high-risk adenoma removal would expectedly drop. This is comparable to stage migration or the Will Rogers phenomenon.[30]

We did not have information on bowel cleansing or caecum intubation rates, factors used as indicators of colonoscopy quality. Colonoscopy have been reported to be more painful[31] and caecal intubation rate lower in women than men,[32] suggesting an average lower quality examination in women. We do, however, have a comparable distribution of proximal adenomas between women and men in the cohort, and it is therefore unlikely that quality and completeness of examination is different for women and men. A more painful experience of colonoscopy might affect surveillance adherence among women, and we did not have data on surveillance. However, any surveillance without adenoma removal cannot change the outcome, and censoring our follow-up at the next adenoma removal did not affect our results. Lastly, we do not have data on serrated polyps. There is conflicting evidence whether serrated polyps are more common in women than in men.[33,34] In this study we cannot determine whether serrated polyps are the cause of the difference in effect of adenoma removal that we find for women and men. Our results, however, indicate that the development of colorectal cancers is different in women than in men, and a possible sex-difference in the serrated pathway should be studied further.

Recent evidence on sigmoidoscopy screening shows a lower benefit in women than in men.[19-21] For colonoscopy screening, potential differences between women and men are still

unclear since none of the studies have sufficiently long follow-up to evaluate the effect on incidence and mortality.[35-37] However, like FOBT and colonoscopy, sigmoidoscopy is considered a screening tool for the whole colorectum, and a positive test leads to follow-up by colonoscopy. Biologically, there is no reason to believe that the development of adenomas diagnosed due to symptoms are different to those diagnosed at screening. Our finding, that women who have had an adenoma removed have increased colorectal cancer incidence and mortality after adenoma removal, are in line with these previous findings on sigmoidoscopy screening, suggesting that the pathogenesis of colorectal cancers may be different in women than in men, avoiding the adenoma-carcinoma pathway.

Our finding of sex-specific differences in risk of colorectal cancer mortality after adenoma removal challenge current surveillance recommendations, which do not consider patient's sex.[17,18] Women who have had adenomas removed still have an increased risk of colorectal cancer death, and do therefore not benefit from intensive surveillance.

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Figure 1. **Standardized incidence ratios (SIR) (A) and incidence-based mortality ratios (SMR) (B) with 95% confidence intervals for colorectal cancer among women and men who had undergone adenoma removal compared to the general female and male population.**

The vertical grey lines indicate SIR and SMR=1.0. Details are given in Tables S3 and S4.

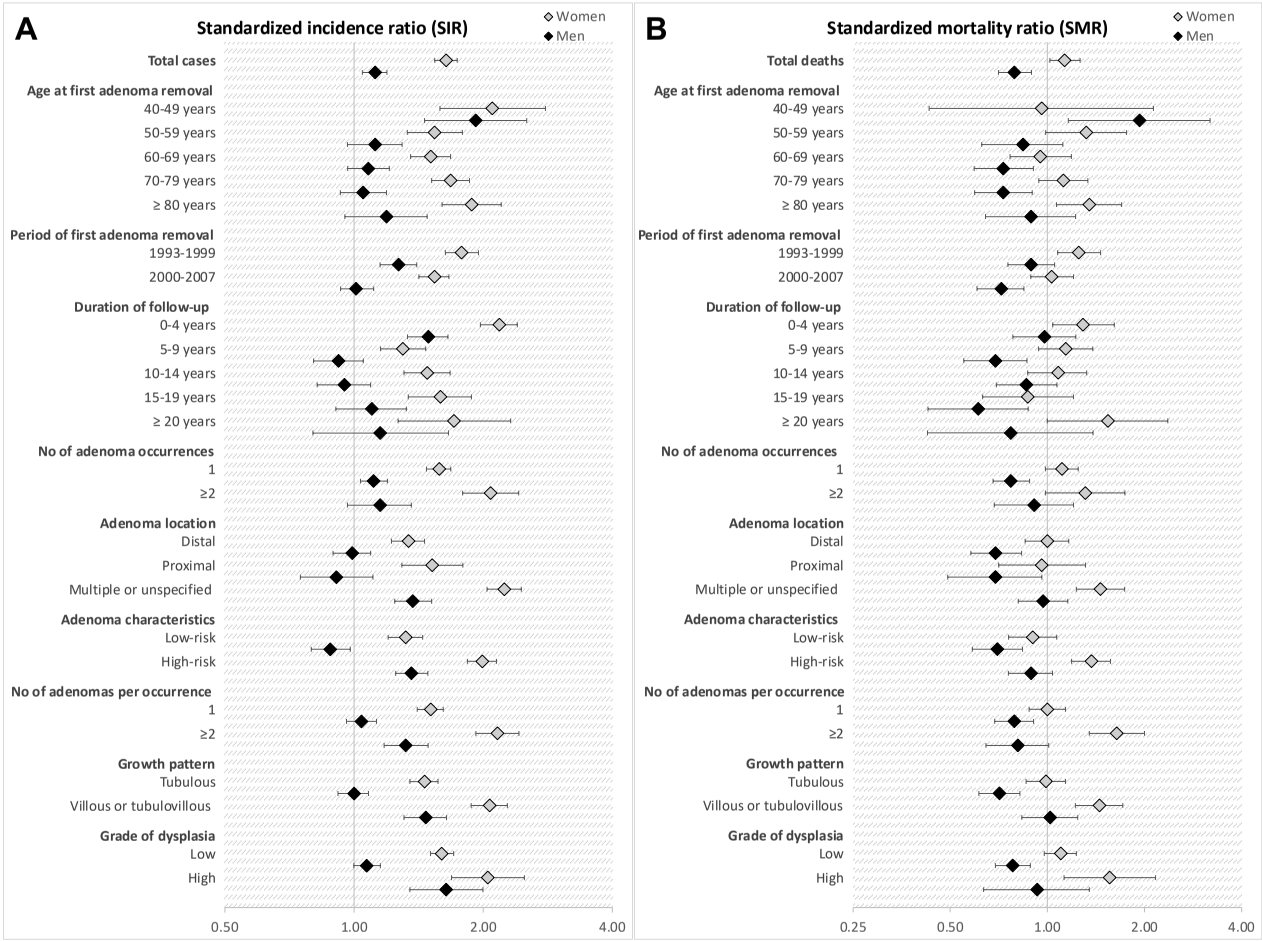


Figure 2. **Absolute risk of colorectal cancer death among women (A) and men (B) during a median of 13.0 years of follow-up after adenoma removal.** The bars show 1) the risk in the general female and male population standardized to the female and male cohort respectively, 2) the cohort of individuals who had undergone adenoma removal, 3) the individuals with low-risk adenomas and 4) the individuals with high-risk adenomas in the cohort. The dashed horizontal line shows the absolute risk of the women and men in the general population as illustrated by the first bar.

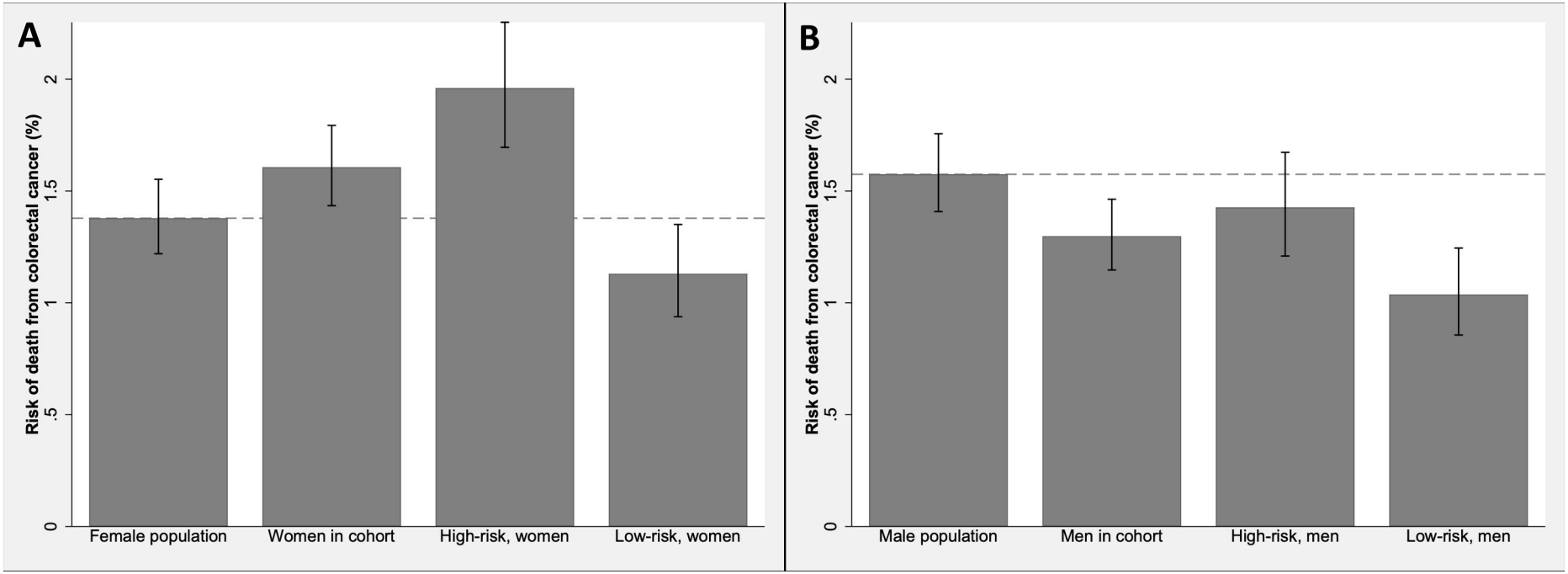
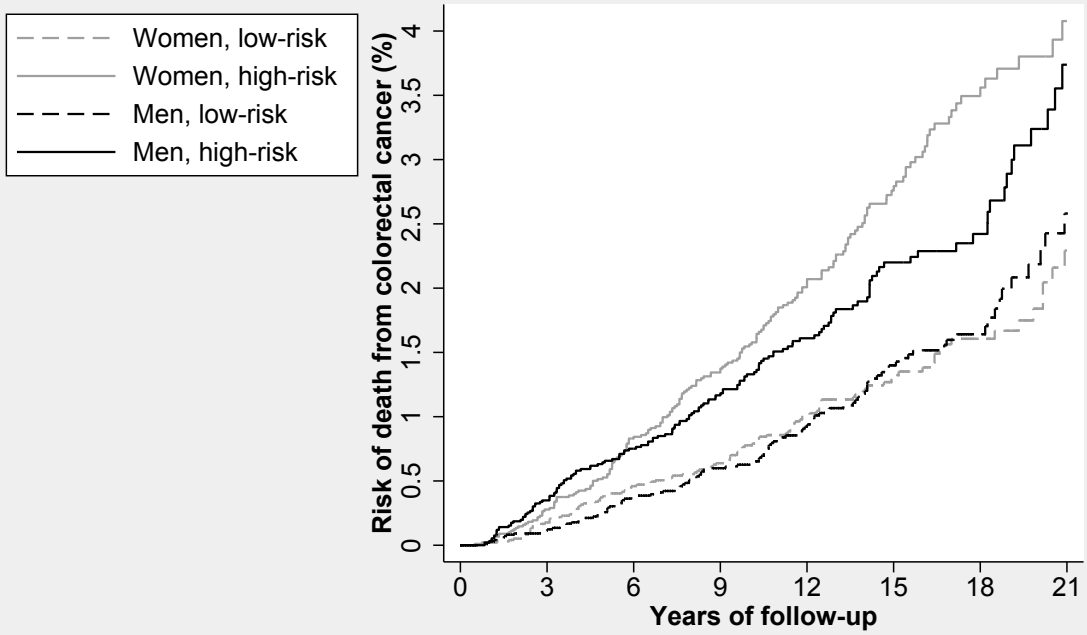


Figure 3. **Cumulative risk of colorectal death among individuals with high-risk and low-risk adenomas.** P value comparing individuals with high-risk and low-risk adenomas with Gray's test <0.001 for both women and men.



No. at risk

Women, low-risk	10116	9457	8763	8003	5996	3641	1821	702
Women, high-risk	9618	8277	7385	6446	4658	2782	1456	627
Men, low-risk	10422	9294	8423	7577	5751	3576	1672	609
Men, high-risk	10152	8367	7230	6213	4391	2546	1233	486

Table 1. **Characteristics of the women and men who had undergone adenoma removal.**

	Women		Men	
Variable	**Individuals**	**Adenomas**	**Individuals**	**Adenomas**
	n (%)		**n (%)**	
Total	19,725	22,017	20,568	23,323
Age at first adenoma removal				
40-49 years	1,869 (9.5)		1,887 (9.2)	
50-59 years	4,254 (21.6)		5,009 (24.4)	
60-69 years	5,311 (26.9)		6,032 (29.3)	
70-79 years	5,339 (27.1)		5,397 (26.2)	
≥80 years	2,952 (15.0)		2,243 (10.9)	
Period of first adenoma removal				
1993-1999	6,863 (34.8)		7,050 (34.3)	
2000-2007	12,862 (65.2)		13,518 (65.7)	
Duration of follow-up				
0-4 years	3,051 (15.5)		4,260 (20.7)	
5-9 years	2,767 (14.0)		3,079 (15.0)	
10-14 years	6,593 (33.4)		6,262 (30.5)	
15-19 years	5,034 (25.5)		5,047 (24.5)	
≥20 years	2,280 (11.6)		1,920 (9.3)	
No. of adenoma occurrences				
1	17,613 (89.3)	17,613 (80.0)	18,052 (87.8)	18,052 (77.4)
≥2	2,112 (10.7)	4,404 (20.0)	2,516 (12.2)	5,271 (22.6)
Adenoma location				
Distal		10,945 (49.7)		10,329 (44.3)
Proximal		2,934 (13.3)		3,119 (13.4)
Multiple or unspecified		8,138 (37.0)		9,875 (42.3)
Adenoma characteristics				
Low-risk		11,357 (51.6)		11,905 (51.0)
High-risk †		10,660 (48.4)		11,418 (49.0)
≥2 adenomas		4,399 (20.0)		6,028 (25.9)
Villous or tubulovillous growth pattern		6,730 (30.6)		6,300 (27.0)
High-grade dysplasia		1,667 (7.6)		1,853 (8.0)

†Modified high-risk criteria: villous growth pattern, high-grade dysplasia, or ≥2 adenomas.

Table 2. **Univariable and multivariable hazard ratios (HR) for death from colorectal cancer among women and men in the cohort.**

	Women				Men			
Variable	**Univariable HR (95% CI)**	**P Value**	**Multivariable HR (95% CI)**	**P Value**	**Univariable HR (95% CI)**	**P Value**	**Multivariable HR (95% CI)**	**P Value**
Age at first adenoma removal								
40-49 years	1.00		1.00		1.00		1.00	
50-59 years	3.72 (1.59-8.72)	0.002	3.65 (1.56-8.54)	0.003	1.29 (0.72-2.31)	0.39	1.27 (0.71-2.28)	0.42
60-69 years	6.16 (2.69-14.14)	<0.001	5.73 (2.50-13.15)	<0.001	2.56 (1.48-4.43)	0.001	2.39 (1.38-4.15)	0.002
70-79 years	14.91 (6.54-33.98)	<0.001	13.36 (5.86-30.47)	<0.001	5.22 (3.00-9.06)	<0.001	4.77 (2.74-8.31)	<0.001
≥80 years	30.65 (13.20-71.18)	<0.001	28.41 (12.21-66.10)	<0.001	10.49 (5.66-19.42)	<0.001	9.91 (5.33-18.42)	<0.001
Period of first adenoma removal								
1993-1999	1.00		1.00		1.00		1.00	
2000-2007	0.75 (0.59-0.94)	0.012	0.77 (0.61-0.97)	0.024	0.68 (0.53-0.87)	0.003	0.70 (0.55-0.90)	0.01
No of adenoma occurrences								
1	1.00				1.00			
≥2	1.07 (0.77-1.48)	0.69			0.98 (0.69-1.38)	0.90		
Adenoma location								
Distal	1.00		1.00		1.00		1.00	
Proximal	1.04 (0.73-1.47)	0.84	1.04 (0.73-1.47)	0.84	1.05 (0.72-1.54)	0.80	1.07 (0.73-1.57)	0.73
Multiple or unspecified	1.54 (1.22-1.95)	<0.001	1.51 (1.18-1.93)	0.001	1.49 (1.16-1.92)	0.002	1.58 (1.22-2.06)	0.001
No of adenomas per occurrence								
1	1.00		1.00		1.00		1.00	
≥2	1.81 (1.43-2.29)	<0.001	1.41 (1.10-1.81)	0.007	1.15 (0.88-1.49)	0.31	0.87 (0.66-1.15)	0.33

Growth pattern								
Tubulous	1.00		1.00		1.00		1.00	
Villous or tubulovillous	1.79 (1.44-2.24)	<0.001	1.52 (1.21-1.91)	<0.001	1.76 (1.37-2.26)	<0.001	1.55 (1.20-2.00)	0.001
Grade of dysplasia								
Low	1.00		1.00		1.00		1.00	
High	1.63 (1.15-2.30)	0.006	1.58 (1.10-2.25)	0.012	1.44 (0.97-2.15)	0.07	1.38 (0.92-2.08)	0.12

Supplementary Material:

Long-Term Colorectal Cancer Incidence and Mortality after Adenoma Removal in Women and Men

Henriette C. Jodal, Dagmar Klotz, Magnhild Herfindal, Ishita Barua, Petter Tag, Lise M Helsingen, Erle Refsum, Øyvind Holme, Hans-Olov Adami, Michael Bretthauer, Mette Kalager, Magnus Løberg

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1. Loberg M, Kalager M, Holme O, Hoff G, Adami HO, Bretthauer M. Long-term colorectal-cancer mortality after adenoma removal. N Engl J Med 2014;371:799-807.
2. Hassan C, Antonelli G, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Update 2020. Endoscopy 2020;52:687-70

Figure S1. **Medical chart study flow chart. A random sample of charts from patients in the adenoma cohort were requested in 10 out of 19 counties in Norway.**

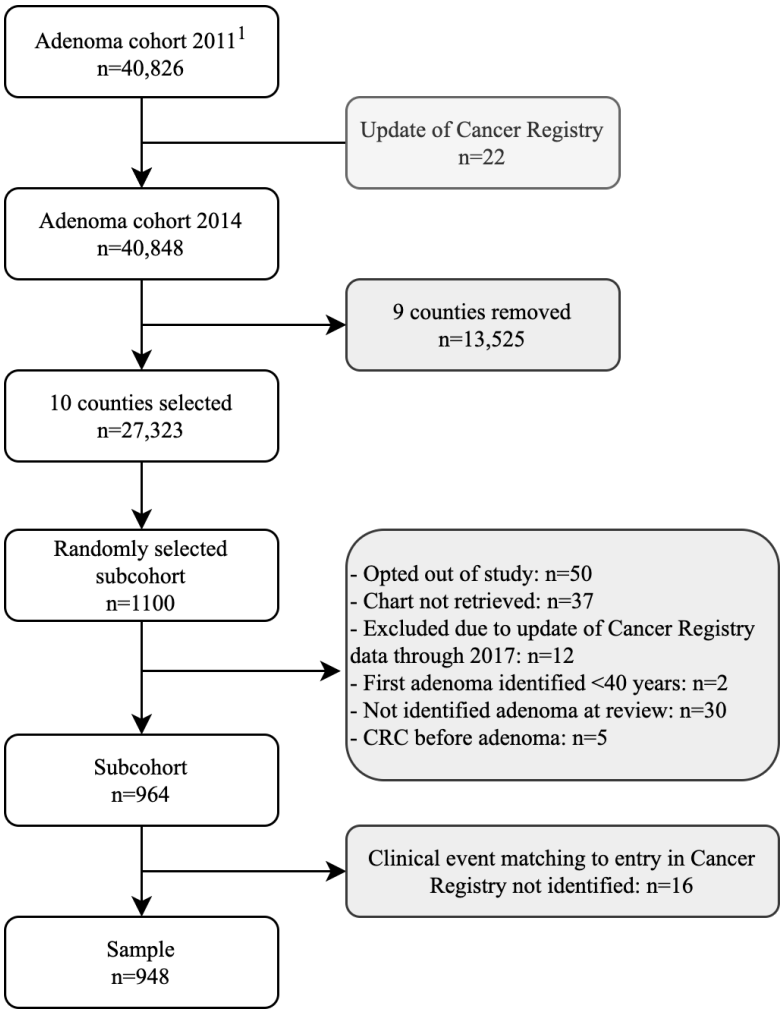
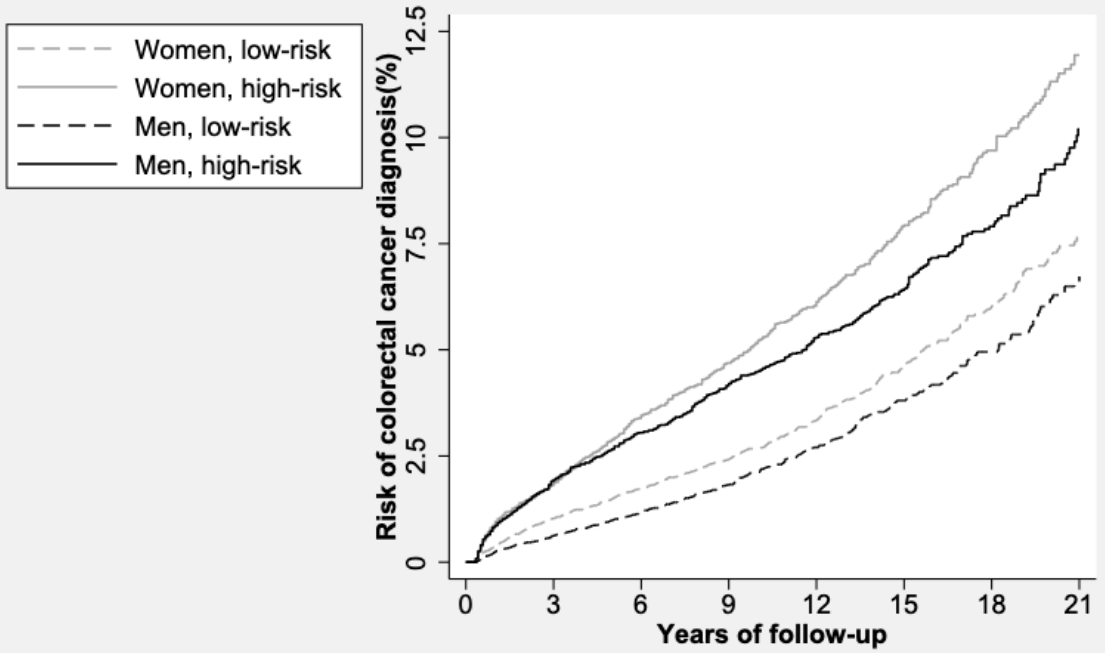


Figure S2. **Cumulative risk of colorectal cancer diagnosis among individuals with high-risk and low-risk adenomas.** P value comparing individuals with high-risk and low-risk adenomas with Gray's test <.001 for both women and men. Cancers occuring within the first four months were regarded as a prevalent cancer.



No. at risk

Women, low-risk	10110	9377	8660	7866	6590	4086	2228	918
Women, high-risk	9615	8140	7189	6240	5033	2977	1681	748
Men, low-risk	10417	9240	8350	7478	6340	3972	2136	783
Men, high-risk	10151	8240	7076	6044	4753	2792	1482	607

Table S1. **Characteristics of the women and men in the chart review study sample, who had undergone adenoma removal.**

	Women		Men	
Variable	**Individuals, n (%)**	**Adenomas, n (%)**	**Individuals, n (%)**	**Adenomas, n (%)**
Total	488	545	460	518
Age at first adenoma removal				
40-49 years	50 (10.3)		34 (7.4)	
50-59 years	112 (23.0)		132 (28.7)	
60-69 years	134 (27.5)		138 (30.0)	
70-79 years	127 (26.0)		116 (25.2)	
≥80 years	65 (13.3)		40 (8.7)	
Period of first adenoma removal				
1993-1999	152 (31.2)		134 (29.1)	
2000-2007	336 (68.9)		326 (70.9)	
Duration of follow-up				
0-4 years	120 (24.6)		133 (28.9)	
5-9 years	65 (13.3)		65 (14.1)	
10-14 years	151 (30.9)		135 (29.4)	
15-19 years	118 (24.2)		110 (23.9)	
≥20 years	34 (7.0)		17 (3.7)	
No. of adenoma occurrences				
1	434 (88.9)	434 (79.6)	405 (88.0)	405 (78.2)
≥2	54 (11.1)	111 (20.4)	55 (12.0)	113 (21.8)
Adenoma location				
Distal		341 (62.6)		281 (54.3)
Proximal		95 (17.4)		131 (25.3)
Multiple or unspecified		109 (20.0)		106 (20.5)
Adenoma characteristics				
Low-risk		275 (50.5)		271 (52.3)
High-risk †		270 (49.5)		247 (47.7)
≥2 adenomas		105 (19.3)		122 (23.6)
≥3 adenomas		27 (5.0)		34 (6.6)
Villous or tubulovillous growth pattern		143 (26.2)		119 (23.0)
High-grade dysplasia		77 (14.1)		78 (15.1)
Size ≥10 mm		167 (30.6)		164 (31.7)

†ESGE risk classification criteria[2]: (tubulo-)villous growth pattern, high-grade dysplasia, ≥10 mm in size, or ≥3 adenomas.

Table S2. **Comparison of the modified and the ESGE adenoma risk classification criteria among women and men in the chart review study.**

		Sample			
		Women		**Men**	
		Low-risk, n (%)	***High-risk*†*, n (%)***	***Low-risk, n (%)***	***High-risk*†*, n (%)***
Cohort	***Low-risk, n (%)***	230 (78.8)	62 (21.2)	225 (79.2)	59 (20.8)
	High-risk ‡***, n (%)***	45 (17.8)	208 (82.2)	46 (19.7)	188 (80.3)

†ESGE high-risk criteria[2]: villous growth pattern, high-grade dysplasia, ≥10 mm in size, or ≥3 adenomas.

‡Modified high-risk criteria: villous growth pattern, high-grade dysplasia, or ≥2 adenomas.

Table S3. **No of observed and expected colorectal cancer cases, and standardized incidence ratio (SIR) for colorectal cancer incidence among women and men.**

	Women			Men		
	No of CRC cases		SIR (95 % CI)	No of CRC cases		SIR (95 % CI)
	Observed	Expected		Observed	Expected	
Total number of CRC cases	1079	659	1.64 (1.54-1.74)	866	775	1.12 (1.05-1.19)
Age at first adenoma removal						
40-49 years	48	23	2.10 (1.59-2.79)	51	27	1.92 (1.46-2.53)
50-59 years	176	114	1.54 (1.33-1.79)	179	160	1.12 (0.97-1.29)
60-69 years	332	220	1.51 (1.36-1.68)	308	285	1.08 (0.97-1.21)
70-79 years	370	220	1.68 (1.52-1.86)	249	247	1.05 (0.93-1.19)
≥ 80 years	153	81	1.88 (1.61-2.20)	79	67	1.19 (0.95-1.48)
Period of first adenoma removal						
1993-1999	484	271	1.78 (1.63-1.95)	397	313	1.27 (1.15-1.40)
2000-2007	595	387	1.54 (1.42-1.66)	469	462	1.01 (0.93-1.11)
Duration of follow-up						
0-4 years	392	180	2.18 (1.97-2.40)	327	220	1.49 (1.33-1.66)
5-9 years	260	200	1.30 (1.15-1.47)	216	235	0.92 (0.81-1.05)
10-14 years	252	170	1.48 (1.31-1.67)	187	197	0.95 (0.82-1.09)
15-19 years	133	84	1.59 (1.34-1.88)	107	98	1.10 (0.91-1.32)
≥ 20 years	42	25	1.71 (1.27-2.32)	29	25	1.15 (0.80-1.66)
No of adenoma occurrences						
1	910	578	1.58 (1.48-1.68)	735	661	1.11 (1.03-1.20)
≥2	169	81	2.08 (1.79-2.42)	131	114	1.15 (0.97-1.36)
Adenoma location						
Distal	486	364	1.34 (1.22-1.46)	377	382	0.99 (0.89-1.09)
Proximal	143	94	1.52 (1.29-1.79)	101	111	0.91 (0.75-1.11)
Multiple or unspecified	450	201	2.24 (2.04-2.46)	388	282	1.37 (1.24-1.52)
Adenoma characteristics						
Low-risk	452	343	1.32 (1.20-1.45)	350	397	0.88 (0.79-0.98)
High-risk	627	316	1.99 (1.84-2.15)	516	378	1.36 (1.25-1.49)
No of adenomas per occurrence						
1	790	525	1.51 (1.40-1.61)	589	566	1.04 (0.96-1.13)
≥2	289	134	2.16 (1.92-2.42)	277	209	1.32 (1.18-1.49)
Growth pattern						
Tubulous	672	462	1.46 (1.35-1.57)	572	574	1.00 (0.92-1.08)
Villous or tubulovillous	407	197	2.07 (1.88-2.28)	294	201	1.47 (1.31-1.64)
Grade of dysplasia						
Low	978	609	1.60 (1.51-1.71)	766	714	1.07 (1.00-1.15)
High	101	49	2.05 (1.69-2.49)	100	61	1.64 (1.35-2.00)

Table S4. **No of observed and expected deaths, and standardized incidence-based mortality ratio (SMR) for colorectal cancer mortality among women and men.**

	Women			Men		
	No of deaths		SMR (95 % CI)	No of deaths		SMR (95 % CI)
	Observed	Expected		Observed	Expected	
Total deaths	328	289	1.13 (1.02-1.26)	275	346	0.79 (0.71-0.89)
Age at first adenoma removal						
40-49 years	6	6	0.96 (0.43-2.13)	15	8	1.93 (1.16-3.20)
50-59 years	46	35	1.32 (0.99-1.76)	46	55	0.84 (0.63-1.12)
60-69 years	80	84	0.95 (0.77-1.19)	86	117	0.73 (0.59-0.91)
70-79 years	125	111	1.12 (0.94-1.34)	91	124	0.73 (0.60-0.90)
≥ 80 years	71	53	1.35 (1.07-1.70)	37	42	0.89 (0.64-1.22)
Period of first adenoma removal						
1993-1999	164	131	1.25 (1.08-1.46)	138	155	0.89 (0.75-1.05)
2000-2007	164	159	1.03 (0.89-1.21)	137	191	0.72 (0.61-0.85)
Duration of follow-up						
0-4 years	79	61	1.29 (1.04-1.61)	76	78	0.98 (0.78-1.23)
5-9 years	103	90	1.14 (0.94-1.38)	76	110	0.69 (0.55-0.86)
10-14 years	88	82	1.08 (0.87-1.32)	82	95	0.86 (0.70-1.07)
15-19 years	37	42	0.87 (0.63-1.21)	30	49	0.61 (0.43-0.87)
≥ 20 years	21	14	1.54 (1.00-2.36)	11	14	0.77 (0.42-1.39)
No of adenoma occurrences						
1	280	253	1.11 (0.99-1.25)	227	293	0.77 (0.68-0.88)
≥2	48	37	1.31 (0.99-1.74)	48	53	0.91 (0.68-1.21)
Adenoma location						
Distal	159	159	1.00 (0.85-1.17)	118	170	0.69 (0.58-0.83)
Proximal	40	42	0.96 (0.71-1.31)	34	49	0.69 (0.49-0.96)
Multiple or unspecified	129	88	1.46 (1.23-1.74)	123	127	0.97 (0.82-1.16)
Adenoma characteristics						
Low-risk	130	144	0.90 (0.76-1.07)	120	171	0.70 (0.59-0.84)
High-risk	198	145	1.37 (1.19-1.57)	155	175	0.89 (0.76-1.04)
No of adenomas per occurrence						
1	229	229	1.00 (0.88-1.14)	198	251	0.79 (0.69-0.91)
≥2	99	60	1.64 (1.35-2.00)	77	95	0.81 (0.65-1.01)
Growth pattern						
Tubulous	195	197	0.99 (0.86-1.14)	179	252	0.71 (0.61-0.82)
Villous or tubulovillous	133	92	1.45 (1.22-1.71)	96	94	1.02 (0.83-1.24)
Grade of dysplasia						
Low	292	266	1.10 (0.98-1.23)	248	317	0.78 (0.69-0.89)
High	36	23	1.56 (1.13-2.17)	27	29	0.93 (0.63-1.35)

Table S5. **No of observed and expected deaths, and standardized incidence-based mortality ratio (SMR) among women and men in relation to the location of the adenoma and the subsequent cancer.**

	Women								
	Proximal cancer			**Sigmoid cancer**			**Rectal cancer**		
Adenoma location	**No of deaths**		**SMR (95 % CI)**	**No of deaths**		**SMR (95 % CI)**	**No of deaths**		**SMR (95 % CI)**
	Observed	**Expected**		**Observed**	**Expected**		**Observed**	**Expected**	
Proximal	32	21	1.51 (1.07-2.14)	6	7	0.87 (0.49-1.93)	7	10	0.68 (0.32-1.42)
Sigmoid	39	34	1.14 (0.83-1.56)	9	11	0.79 (0.41-1.52)	10	17	0.59 (0.32-1.10)
Rectum	57	50	1.15 (0.88-1.49)	7	17	0.42 (0.20-0.89)	44	25	1.77 (1.32-2.38)
Multiple	3	2	1.94 (0.63-6.02)	0	1	N/A	0	1	N/A
Unspecified	57	28	2.02 (1.56-2.62)	9	9	0.97 (0.50-1.86)	23	14	1.66 (1.11-2.50)
	Men								
	Proximal cancer			**Sigmoid cancer**			**Rectal cancer**		
Adenoma location	**No of deaths**		**SMR (95 % CI)**	**No of deaths**		**SMR (95 % CI)**	**No of deaths**		**SMR (95 % CI)**
	Observed	**Expected**		**Observed**	**Expected**		**Observed**	**Expected**	
Proximal	27	21	1.29 (0.89-1.89)	7	10	0.68 (0.32-1.42)	8	17	0.47 (0.23-0.94)
Sigmoid	27	28	0.96 (0.66-1.40)	4	14	0.28 (0.11-0.75)	11	23	0.47 (0.26-0.85)
Rectum	38	46	0.83 (0.60-1.14)	10	23	0.44 (0.23-0.81)	36	38	0.95 (0.68-1.31)
Multiple	1	2	0.52 (0.07-3.71)	0	1	N/A	1	2	0.64 (0.09-4.56)
Unspecified	43	33	1.29 (0.96-1.74)	14	17	0.84 (0.50-1.41)	21	28	0.76 (0.50-1.17)

Table S6. **No of observed and expected deaths, and standardized incidence-based mortality ratio (SMR) for colorectal cancer mortality among women and men, limited to 10 years of follow-up after adenoma removal.**

	Women			Men		
	No of deaths		SMR (95% CI)	No of deaths		SMR (95% CI)
	Observed	Expected		Observed	Expected	
Total deaths	215	160	1.34 (1.18-1.54)	183	197	0.93 (0.81-1.08)
Age at first adenoma removal						
40-49 years	2	2	0.92 (0.23-3.70)	7	2	3.05 (1.46-6.40)
50-59 years	24	13	1.78 (1.19-2.66)	30	21	1.44 (1.01-2.06)
60-69 years	43	37	1.17 (0.87-1.57)	47	56	0.84 (0.63-1.12)
70-79 years	81	67	1.22 (0.98-1.51)	64	83	0.77 (0.60-0.99)
≥ 80 years	65	41	1.58 (1.24-2.02)	35	35	1.01 (0.73-1.41)
Period of first adenoma removal						
1993-1999	91	58	1.57 (1.28-1.92)	85	72	1.17 (0.95-1.45)
2000-2007	124	102	1.22 (1.02-1.45)	98	124	0.79 (0.65-0.96)
Duration of follow-up						
0-4 years	80	62	1.30 (1.05-1.62)	79	78	1.02 (0.82-1.27)
5-9 years	135	99	1.37 (1.16-1.62)	104	119	0.87 (0.72-1.06)
No of adenoma occurrences						
1	188	143	1.32 (1.14-1.52)	156	171	0.91 (0.78-1.07)
≥2	27	17	1.58 (1.08-2.30)	27	26	1.06 (0.72-1.54)
Adenoma location						
Distal	119	88	1.35 (1.13-1.61)	91	97	0.94 (0.76-1.15)
Proximal	29	25	1.18 (0.82-1.69)	26	30	0.86 (0.59-1.27)
Multiple or unspecified	67	47	1.42 (1.12-1.81)	66	69	0.95 (0.75-1.21)
Adenoma characteristics						
Low-risk	79	78	1.02 (0.81-1.27)	68	93	0.73 (0.58-0.93)
High-risk	136	82	1.65 (1.40-1.95)	115	104	1.11 (0.92-1.33)
No of adenomas per occurrence						
1	154	127	1.22 (1.04-1.42)	130	141	0.92 (0.78-1.09)
≥2	61	33	1.83 (1.42-2.35)	53	56	0.95 (0.73-1.25)
Growth pattern						
Tubulous	123	107	1.15 (0.96-1.37)	106	139	0.76 (0.63-0.92)
Villous or tubulovillous	92	53	1.73 (1.41-2.13)	77	58	1.34 (1.07-1.67)
Grade of dysplasia						
Low	186	147	1.26 (1.09-1.46)	164	179	0.92 (0.79-1.07)
High	29	13	2.26 (1.57-3.25)	19	17	1.09 (0.69-1.70)

Errata list

Name of candidate: Henriette Cecilie Jodal

Title of thesis: The Risk of Colorectal Cancer Incidence and Mortality after Screening and Adenoma Removal

Abbreviations for type of corrections:

- cor: correction
- cetfl: change of page layout or text format

Page	Line	Original text	Type of correction	Corrected text
10	6	"… Per Olav Vandvik"	cor	"… Per Olav Vandvik, Louise Emilsson"
13	22	"FOBTs…"	cor	"Faecal occult blood tests (FOBT)…"
14	21	"… the definition of a positive test required FOBT may be…"	cor	"… the definition of a positive test may be…"
17	3	"… developing colorectal."	cor	"… developing colorectal cancer."
31	22	"… excluding cancers diagnoses…"	cor	"… excluding cancers diagnosed…"
33	18	"… we a randomly selected…"	cor	"… we randomly selected…"
35	13	"… in random-effects models."	cor	"… in fixed-effects models."