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Once-only Colonoscopy or biennial Fecal Immunochemical Testing for colorectal cancer (SCREESCO) – Baseline Report of a Randomised Controlled Trial

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Research in context:

Evidence before this study

Randomised evidence reviewed in several meta-analyses shows that screening with guaiac-based tests for fecal occult blood (gFOBT) or flexible sigmoidoscopy (SIG) reduce colorectal cancer (CRC) mortality. We searched PubMed on October 6, 2021, using the following search terms: colorectal cancer # screening # randomised controlled trials (RCT), and summarized the results from RCTs. The IARC handbook of cancer prevention vol 17 (2019): Colorectal cancer screening also served as source of information. In many countries CRC is a serious health problem, being the second and third most common killing cancer for men and for women in Europe. Hence, a majority of industrialized countries have guidelines for programs to detect CRC early. Screening programs have increasingly started to use high sensitive immunochemical tests (FIT) instead of gFOBT or colonoscopy in the theoretical hope of improving detection rates of premalignant or malignant lesions and after promising results in observational studies. The effectiveness of using these tests rather than gFOBT or SIG has however not been quantified in randomised trials and many questions remain unanswered about e.g. their influence on participation, side-effects, if a lesser effectiveness in women for SIG can be overcome, and if high quality colonoscopy can be upheld under routine practice.

Added value of this study

SCREESCO is one of four ongoing large trials in the problem field, but is unique in that it studies the effects of both a one-time FIT screening (60,300 invited to a biennial FIT testing) and a one-time direct colonoscopy (31,440 invited) compared to controls offered standard diagnostic pathways (186,840). This report, from the two intervention arms after completion of accrual and screening, focuses on participation proportion, baseline findings and adverse

events from March 2014 to December 2020 in the two intervention arms. The findings contrast participation in two different tests in the same population: 56% of those invited to FIT testing and 35% of those invited to colonoscopy participated. The study also give evidence on colonoscopy quality in a clinical routine setting. There were 15 major bleeds and two perforations in 16,555 colonoscopies. Furthermore, the pattern of detection of pre- and malignant lesions is of interest for future screening programs. In intention to screen analyses the detection of CRC was not statistically different in the two intervention arms; in the FIT arm 16 advanced adenomas/1,000 and in the colonoscopy arm 20/1,000 randomized were detected. Colonoscopy detected more adenomas at all colo-rectal locations, but especially so at the right side; in analyses stratified on gender, these differences in adenoma-detection was especially marked for women.

Implications of all the available evidence

The participation and findings to date indicates that SCREESCO will be able to answer if the one-time screening concept can reduce CRC morbidity and mortality to an acceptable degree, the one-time screening being attractive both for individuals and for health care administration. The colonoscopy quality, the overall diagnostic yield and the low number of adverse events in a routine clinical setting indicates that the SCREESCO design can be transferred to a population-screening service. The possible consequences of study arm-, gender- and anatomical location-specific adenoma detection rates will inform future early detection programs and a previously noted less effective screening by SIG for women may be overcome.

Summary

Background Currently, screening for colorectal cancer employs lower gastrointestinal endoscopy or stool-based tests. Randomised evidence for primary colonoscopy to reduce mortality in colorectal cancer is lacking. We present the baseline results of SCREESCO (SCREEning of Swedish COlons), a nationwide randomised trial investigating the effect of screening on mortality in colorectal cancer.

Methods Residents in 18 of 21 counties in Sweden who were turning 60 years old in the year of randomisation were identified from a population register maintained by the Swedish tax agency. A statistician with no further involvement in the trial used a randomised block method to allocate individuals to once-only colonoscopy, two rounds of FIT (OC-Sensor) 2 years apart, or to control (no intervention), with a ratio of 1:6 for once-only colonoscopy versus control and 1:2 for FIT versus control. The primary endpoints of the trial are colorectal cancer-related mortality and colorectal cancer incidence. Here, we report participation rates, baseline findings, and adverse events from March, 2014, to December, 2020, in the two intervention arms after completion of accrual and screening. Analyses were done on an intention-to-screen basis with all randomised to the respective study arm as denominator. This study is registered with ClinicalTrials.gov, number NCT02078804.

Findings Between March, 2014, and December, 2020, 31 440 individuals were invited to the colonoscopy arm, 60 300 to the FIT arm, and 186 840 to the control group. 10 679 (35%) of 30 400 individuals invited to undergo colonoscopy participated. 33,383 (56%) of 60 137 individuals who received a mailed FIT test participated in the FIT arm. In the intention-to-screen analysis, 49 participants (1·6 per 1000) in the colonoscopy arm versus 121 (2·0 per 1000) in the FIT arm (relative risk 0·78, 95% CI 0·56–1·09) had colorectal cancer. Advanced adenomas were detected in 637 individuals (20 per 1000) by colonoscopy and 968 (16 per 1000) by FIT (relative risk 1·27, 95% CI 1·15–1·41). Colonoscopy detected more right-sided

advanced adenomas than FIT. There were two perforations and 15 major bleeds in 16 555 colonoscopies.

Interpretation The diagnostic yield and the low number of adverse events indicate that the SCREESCO logistics can be transferred to a population-based screening service should a benefit in disease-specific mortality subsequently be shown.

Funding Grants from eighteen Swedish regions, the Stockholm County Council, Regional Cancer Center Mellansverige, the Swedish Cancer Society, Aleris Research and Development Fund and Eiken Chemical of Japan.

Introduction

Primary colonoscopy for screening of colorectal cancer lacks evaluation in randomised controlled trials (RCTs). There are two ongoing RCTs investigating colonoscopy versus faecal immunochemical testing for hemoglobin (FIT), COLONPREV (1) and CONFIRM (2), and one RCT of colonoscopy versus no intervention, NordICC (3). So far, none of these study teams have published data on colorectal cancer mortality, although COLONPREV and NordICC have presented their baseline data. The nationwide RCT SCREESCO (SCREEning of Swedish COlons) compares, in a previously untested strategy, no intervention to colorectal screening, involving either a once-only invitation to colonoscopy or invitations to two rounds of hypersensitive FIT using two-stool samples 24 months apart, in individuals aged 60 years. The purpose is to evaluate the effectiveness of the two screening interventions to reduce colorectal cancer mortality in regions covering two thirds of the Swedish population which at the start of the study were not being offered an organized program of colorectal cancer screening.

In this report we present participation, adverse events and diagnostic data in the two screening arms up to the completion of the second FIT round.

Methods

Study design and participants

SCREESCO is a randomised controlled trial conducted in 18 of 21 regions of Sweden, all naive to co-ordinated colorectal cancer screening programs and comprising 74.5% of the total population of Sweden. Participants were identified from a population register maintained by the Swedish tax agency and randomly assigned to one of three groups: invitation to once-only colonoscopy, invitations to two high-sensitivity FIT, or no intervention. All individuals were aged 60 years at the time of invitation to the intervention; individuals in the control group had the same age. Exclusion criteria were a prior diagnosis of colorectal and/or anal cancer and allocation to the ongoing NordICC trial (3). All individuals undergoing colonoscopy signed a consent form for the procedure and for biobanking purposes. Those allocated to invitation to FIT consented by sending in the test. Individuals randomised to the control arm were not individually informed about participation in the study.

The Ethics Committee at Karolinska Institutet approved the study (2012/2058-31/3).

Randomisation

Full details of the randomisation procedure are shown in the appendix. A statistician at Regional Cancer Center Mellansverige (Sweden) with no further involvement in the study used Stata (version 13.1) for Power calculations and SAS (9.4) for randomisation to randomly allocate individuals to once-only colonoscopy, invitation to two rounds of FIT two years apart, or control. Randomisation was performed separately for each birthyear 1954-

1958, and stratified by region of residence (county), and sex. Individuals were randomised with a ratio of 1:6 for once-only colonoscopy versus control and 1:2 for FIT versus control within each such strata, maintaining balance by randomly permuting the list of eligible individuals and assigning them proportionally to each study arm. The total number of randomised individuals in each year was determined by the Power calculations, and the distribution of these over region and sex was defined according to the distribution of the population of 60-year olds in participating regions during year 2012, based on numbers from Statistics Sweden (https://www.scb.se/en/). Follow-up began from the day of allocation.

Procedures

All invitees received a letter describing the study and a leaflet about colorectal cancer and screening. A reminder was sent after eight weeks. In the colonoscopy arm, a second letter offered a scheduled time for a colonoscopy or to arrange a time by phone.

In the FIT group, the letter included kits for stool samples. A quantitative FIT (OC-Sensor®, Eiken Chemical with support from Eiken Chemical of Japan and its local representatives for FIT kits and laboratory supplies) using two-stool samples with separate kits for each was employed per cycle; kits returned within six months was counted as screening participation. The invitees were instructed to take samples from two different bowel movements, preferably not on the same day. One central laboratory performed all FIT analyses using a single OC-Sensor Diana automated analyzer. A hemoglobin concentration of $\geq$10 μg/g of faeces defined the cut-off for positivity. In each round, one or more positive FIT triggered an invitation to a colonoscopy identical to that offered to the colonoscopy group. In the absence of a response, the invitee received one reminder by telephone and subsequently one by mail. All individuals

in the FIT arm, except those requiring colonoscopy surveillance after adenoma removal or after a colorectal cancer diagnosis, were offered a repeat FIT after two years, irrespective of participation the first FIT round or if the result was negative or positive. Individuals in both study arms were offered an opportunity to submit samples for biobanking, but acceptance was not mandatory for participation. The definition of participation in once-colonoscopy was having performed at least one colonoscopy, and in FIT as having returned at least one FIT-test for analysis.

33 hospitals performed the colonoscopies. If the participant at the consultation at the screening unit was deemed too frail to undergo a colonoscopy, the attending physician made the decision to abstain from the procedure. The 146 endoscopists, gastroenterologists, surgeons or nurses, were certified by having performed >100 colonoscopies per year and having performed >1,000 in total before the study. The protocol recommended the use of a high-volume split laxative for bowel cleansing, carbon dioxide insufflation during the examination, and removal and retrieval of all lesions for histology. The endoscopists recorded size and location (right-sided (proximal to the splenic flexure), left-sided, or rectal) of all lesions. A Boston Bowel Preparation Score of two or more in each bowel segment defined a clean bowel (4).

Using the WHO histopathology classification, polyps were categorized as adenomas, serrated polyps, or inflammatory polyps (5). Advanced adenomas were adenomas measuring ≥10mm in diameter, or having a villous component, or with high-grade dysplasia. Colo-rectal cancers were staged according to UICC-stages. Disease staging for this report is based on the reports from the screening centers. We recorded sessile serrated polyps as a separate group, defined as advanced at a diameter of 10mm or more. The endoscopy units reported severe adverse events that occurred within 30 days of the colonoscopy. We searched the Causes of Death Register for deaths within 30 days of the colonoscopy. Two nurses monitored the process at a

central office. When the screening interventions were completed, a study nurse together with the corresponding author checked the case form reports for completeness or inconsistencies, and if needed, additional information was obtained from the screening units.

Follow-up will employ the Swedish registers in-patient health-care, for cancer and causes of death. The registers are currently only complete to the end of 2019 and colorectal cancer mortality is not included in this report. Neither can we, at the time of writing, report on the occurrence of colorectal cancer or colonoscopy activity in the control group or in non-participants in the intervention arms.

Outcomes

The primary endpoint of the trial is disease-specific mortality due to colorectal cancer and incidence in colorectal cancer, where each of the two intervention arms are compared with the control group.

Secondary endpoints are: to study compliance with the screening program and what factors are of importance for the adherence rate; to study health economy and costs for colorectal cancer screening; to study the emotional impact of screening on participants and non-participants including eventual change in lifestyle after invitation and/or participation; to study quality control aspects and side effects of screening with colonoscopy; to study pathology by means of quality registries and digital pathology; to study surveillance strategies for adenomas found at colonoscopy; to study associations of DNA in blood with findings at colonoscopy; and to study the flora of fecal bacteria among participants and outcome of FIT and colonoscopy.

This report describes the participation, occurrence of serious adverse events and diagnostic yield of the screening procedure in the intervention arms. Results for the primary or

secondary outcomes for the SCREESCO study are not yet available. We provide participation proportion by study arm, probability of being detected with a colorectal cancer or a polyp and risk of an adverse event and we provide relative and absolute differences between the study arms for these measures.

We report the findings on the intention-to-screen level (i.e. with all randomised to the respective arm as denominator) and on the per-protocol level (i.e. with those participating in screening in the respective arm as denominator) with the cohort size for each described in figure 1 and tables 1 and 2. For each level, we present results for cancer, advanced adenoma, non-advanced adenoma, having three or more adenomas and sessile serrated polyps ≥10mm, and the anatomical location of the lesions. We report once-colonoscopy compared to the result of invitation to two FIT two years apart, i.e. the results in the FIT arm are pooled from two FIT rounds.

Statistical analysis

The sample size calculation was based on the primary endpoint mortality in colorectal cancer. The original sample size target was 201,000 individuals based on an assumed 1% cumulative colorectal cancer mortality for a follow-up between 60 and 75 years of age. We revised the target in 2015 due to lower uptake of screening than anticipated. In the revised study plan, we assumed a 15% reduction in disease specific mortality by 15 years as a minimal clinically important effect in those invited to FIT and based on a participation of 50%. We further assumed a 17.5% mortality reduction in those invited to colonoscopy based on 35% participation. Inclusion of 31,140 in the colonoscopy arm and 60,300 in the FIT arm, to be compared with 186,840 and 120,600, respectively, in the control arm, allow differences to be detected at two-sided 2.5% significance level with 80% power for the comparison of FIT versus control and 73% power for the comparison of colonoscopy versus control. The

significance level was adjusted for two comparisons according to the Bonferroni method. In the supplementary material there is a document that details the calculations to dimension the study.

Chi-square tests were applied for the differences in participation. Adverse events was recorded on the per protocol level in the once-colonoscopy group, and for those in the FIT arm who participated in a work-up colonoscopy.
To explore differences in patterns of diagnostic yield in the intervention arms, we report the adjusted relative risks with 95% confidence intervals (CI) estimated in binary regression models with log link, i.e. a log-linear model in the probability of the outcome.

Due to differences in participation between women and men, the estimates were adjusted for sex on the per-protocol level, and on the intention-to-screen level we assessed if there was an effect modification of sex. We compared the diagnostic yield between males and females by adding an interaction term to the regression model. The interaction was estimated by a ratio of the relative risks for men versus women, presented with 95% CI and p-value. Fisher's exact test was used to compare cancer stage between the FIT and colonoscopy groups, due to the low numbers of stage IV cancers. SCREESCO has the ClinicalTrials.gov number NCT02078804. We performed the analyses using R version 4.1.0 (www.r-project.org).

Role of funding source:

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AF, MW, LH and RH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors made the decision to submit for publication.

Results

Population and participation

The study started in March 2014 and finished recruitment and one screening round including both invitations to FIT testing in December 2020. From those born in each of 1954, 1955, 1956, 1957 and 1958, 201,000 (first three years) and subsequently 77,280 individuals were randomly selected (278,280 in total).

We included 278,280 individuals. Of these, 31,140 and 60,300 were randomised to invitation to colonoscopy or invitation to two rounds of FIT, respectively (Figure 1). In the colonoscopy arm 10,679 (35.1%) of the 30,400 invited participated. Participation for men and women was 5,507 of 15,166, 36.3% (95% CI, 35.6-37.1) and 5,172 of 15,234, 34.0% (95% CI, 33.2-34.7), respectively (p<0.0001, chi-square test). Of the 60,137 individuals who received a mailed FIT-test, 33,383 participated in one or both years, giving a participation of 55.5%. Participation in first-only was 4,086 of 60,137 (6.8%), second-only 4,408 of 60,137 (7.3%), or both FIT tests were 24,889 of 60,137 (41.4%). Participation in men was 15,519 of 30,046 (51.6%) (95% CI, 51.1-52.2) and in women 17,864 of 30,091 (59.4%) (95% CI, 58.8-59.9), (p<0.0001). Of the 6,471 with a positive FIT, 5,876 (90.8%) underwent a work-up colonoscopy in which participation for men and women was 3,069 of 3,369 (91.1%) and 2,807 of 3,102 (90.5%), respectively, (p=0.43, chi-square test).

Overall performance

Certified endoscopists performed >99% of the 16,555 colonoscopies. In the FIT arm, 410 of 6,471 individuals (6.3%) participated in a colonoscopy in both rounds. The bowel preparation was satisfactory in 16,224 of 16,555 (98.0%) including 139 individuals re-scheduled following an inadequate bowel preparation. The crude caecal intubation rate as reported on the colonoscopy form was 16,860 of 16,555 (95.8%) (96.3% in the colonoscopy arm and 95.0% in the FIT arm). Eight percent (1,270 individuals of 16,555) of colonoscopy

participants required sedation with propofol; 44.6% (7,367 individuals of 16,555) required benzodiazepine and/or opioids, and 47.1% (7,802 individuals of 16,555) did not need sedation or analgesics. Of the 710 (4.2% of 16,555) participants with incomplete colonoscopies, 261 (36.8% of 710) underwent a CT colonography and 449 of 710 (63.2%) individuals declined further examinations.

The polyp detection rate (PDR) was 45% in the colonoscopy arm and 58% for the colonoscopies in the FIT arm. The median adenoma detection rate (ADR) for the endoscopists in the colonoscopy arm was 20% (interquartile range for the endoscopists 12-28%), and 34% (interquartile range 25-43%) in the FIT arm.

Adverse events

Units reported severe adverse events in 27 (0,16% of 16,555) participants in a colonoscopy. Due to the few events, we report all in detail rather than graded on a group level. Four were related to the bowel cleansing: ileus (two), dehydration and hypoglycemia. Two perforations, both in therapeutic FIT colonoscopies, and one individual with post-polypectomy coagulation syndrome necessitated admission to hospital. In 15 cases, all but one in therapeutic colonoscopies (three in once-only colonoscopy and 12 in FIT), a major bleed was reported, of which seven needed transfusion and three needed endoscopic clipping; five were only observed in hospital. In total, a perforation occurred in one per 8,300, and major bleed in one per 1,100 colonoscopies. On the intention to screen level, there were 1:5,000 bleeds and 1:30,000 perforations in the FIT arm, and in the colonoscopy arm there were 1:15,500 bleeds. A vasovagal reaction occurred in one case.

Within thirty days of the endoscopy, one minor stroke, one episode of atrial fibrillation and one ruptured aortic aneurysm occurred. There was only one death, which followed a

pulmonary embolism in a man with metastatic cancer occurred in the FIT arm day 15 after the colonoscopy.

Diagnostic yield

In the intention-to-screen analysis (Table 1), colorectal cancer was detected in 49 (1.6/1,000) individuals in the colonoscopy arm and 121 (2.0/1,000) in the FIT arm (relative risk: 0.78; 95% CI, 0.56-1.09). The corresponding findings for advanced adenomas were 637 (20.5/1,000) and 968 (16.1/1,000) (relative risk: 1.27; 95% CI, 1.15-1.41) for colonoscopy compared to FIT. Colonoscopy also detected more non-advanced adenomas (relative risk: 2.82; 95% CI, 2.63-3.02) and more right sided lesions but not left-sided or rectal advanced adenomas (Table 1).

The same pattern was seen on the per-protocol level (Table 2), with a similar yield of cancer in the colonoscopy and FIT arms (4.6 and 3.6/1,000 respectively), and a higher yield for advanced and non-advanced adenomas for colonoscopy (59.6 versus 29.0/1,000 participants for advanced adenoma). On this level of comparison, colonoscopy detected more adenomas irrespective of location, but with still some dominance for the right side. Figure 1 records the yield in FIT-round 1 and 2 separately. The analyses in Table 1 and 2 were repeated with adjustment for region and sex with virtually the same results (data not shown).

On the colonoscopy level, the FIT arm had a higher yield than the colonoscopy arm for any type or location of lesion. To find one cancer, 218 colonoscopies had to be performed in the colonoscopy arm and 49 in the FIT arm; the corresponding figures for advanced adenoma were 17 and 6 respectively (Supplemental Table 1).

Four of the polyp cancers, early cancers located to a stalked or broad-based polyp, were reported as intramucosal cancer with “budding” to the muscularis mucosae, and they were

treated as adenocarcinoma Stage I. There was no evidence of a difference in the distribution of stage in cancers detected by FIT and colonoscopy (Table 3).

In analyses stratified by sex, the relative risk for colonoscopy versus FIT to find advanced adenomas on the intention-to-screen level was 1.27 for men as well as for women. (Supplemental Table 2). The corresponding findings for sessile serrated polyps was 1.94 and 3.40. The same pattern appeared on the as screened level (Supplemental Table 3). In an analysis of interaction between sex and randomisation arm, the relative risk for right-sided advanced sessile serrated polyps among men was 46% lower compared to women; RRmen/RRwomen=0.57 (95% CI: 0.37-0.87, p = 0.0090) (Supplemental Table 2). Similar results with somewhat different effect size was seen on the per-protocol level.

Discussion

In this baseline report after finalizing recruitment and one screening round of SCREESCO, a nationwide randomised controlled screening study, we report data on the participation and the yield in the colonoscopy arm and the FIT arm. At the end of recruitment and one screening round of SCREESCO, 35% of those invited to a once-only colonoscopy participated, and 56% participated in the FIT arm. Units achieved satisfactory bowel preparation and caecal intubation. Perforations and major bleeds were few. Cancer findings were similar in the two arms. Diagnosis of advanced adenoma was more common in the colonoscopy arm than in the FIT arm.

The study has several strengths. This randomised design with a control group with no intervention in a screening naïve setting, and the large size makes the study unique (1-3, 6). Sweden has reliable national registers to facilitate future follow-up, including systematic follow-up of the results of colorectal cancer screening programs implemented gradually from

2021. The latter register together with a national clinical database for colonoscopy enables a control of contamination of further screening of the study participants. The large group of certified endoscopists, and the differences between the units' organization mirror reality, yielding results generalizable to future routine screening practice, further supported by a low frequency of adverse events (7).

A limitation in the current report is that adverse events may have been treated at other departments than the screening unit and may not have been reported. These will, however, be captured by follow-up using health care registers. Furthermore, the colonoscopy quality is self-reported by the endoscopists, but image documentation is available for future evaluation.

The screening interventions were designed with feasibility and cost-effectiveness in mind, and the FIT arm entails a new approach with only one repeat FIT at two years. A high-sensitive FIT at a two-year interval is intended to be similar to once-only colonoscopy in detecting the relevant lesions to prevent colorectal cancer death in a 10 to 15-year time frame (8). In an experimental epidemiological study, a decrease in mortality appeared already after seven years (9), something that may support our screening model. A once in a lifetime invitation to screening is administratively simple and appealing to the population. When the study was designed in 2012, EU recommended evidence-based population screening by feacal occult blood test in the ages 50-74 (9), hence, our choice to invite at age 60. Recent trends in colorectal cancer incidence and modelling studies argue for a first screening at 55 or lower (10, 11). The follow-up of the SCREESCO study will add new perspectives regarding screening program design.

Uptake is of the utmost importance for the effectiveness of an organized screening program in reducing colorectal cancer mortality at a population level, and a low uptake is one of the main problems in colorectal cancer screening in many settings (12). A valid comparison in terms of program efficiency of two strategies that have different levels of compliance necessitates an intention to screen approach. The per-protocol analysis is subject to selection bias and require adjustment for risk factors on an individual level, information which is not available at this stage of the study, but will be possible by follow-up in national health registers.

The participation in the colonoscopy arm was lower than in the FIT arm, especially for women, but higher than or in line with other studies (1, 3), albeit lower compared to a recent Chinese study (6). In the FIT group, the adherence to colonoscopy following the positive FIT was high, 90.1% (13). Our results indicate that in the Swedish cultural setting and public understanding of colorectal cancer, similar to that in some other countries (3, 14), the processes for invitation and screening used in the SCREESCO study can be translated into a routine colorectal cancer-screening program to achieve what is today considered to be an acceptable level of compliance for program effectiveness. However, there is still a great need to research and test methods to increase uptake for early detection of bowel cancer.

The adenoma detection rate is in line with the recommendations for FIT-based screening (15). The future incidence of colorectal cancers in the screened population will reveal if our adenoma detection rate is sufficient for the aims of the program (16). As expected, the adenoma detection rate varied among endoscopists. However, the caecal intubation rate was in line with recommendations for screening colonoscopies (13, 17).

The frequency of adverse events is comparable to or lower than in other studies (18-20). This may in part be due to infrequent use of general anaesthesia, a factor identified as a risk factor for perforation (21).

Detection of cancers was similar in the two intervention arms in the intention-to-screen and in the per-protocol analysis, similar to the findings in the study by Quintero et al (1) but contrary to a Chinese study (6) where colonoscopy had a higher yield. However, polypectomy is the main effector in colorectal cancer prevention (22), and the different capacity of the SCREESCO study arms to find premalignant lesions is likely to have implications for the long term colorectal cancer mortality (23, 24).

Colonoscopy had a higher yield than FIT of advanced, non-advanced and multiple adenomas, and sessile serrated polyps, especially for right-sided lesions and for such lesions in women. Individuals with a history of sessile serrated polyps, especially when large and right-sided, have increased colorectal cancer mortality (25, 26) and seem to benefit less from FIT screening (27). The findings for women accord with a lower reduction in colorectal cancer mortality in women both by faecal blood tests and by flexible sigmoidoscopy (28, 29). Future analyses of colorectal cancer incidence and mortality will tell if and how our findings translate to screening efficacy. Our cut-off for FIT positivity is very low, and we can determine if the intervention arms both have a preventive effect on the serrated pathway to colorectal cancer and we will study if the SCREESCO intervention design overcomes differences by gender.

The pattern of diagnostic yield at the colonoscopy level of comparison of the study arms is driven by the selective investigation of test-positive individuals in the FIT arm. As a consequence, fewer colonoscopies had to be done to detect one lesion in the FIT arm, which will be one important parameter in future economical evaluations of screening strategies.

Future cost-benefit evaluations will include patient reported outcomes of participation – so me results are already published (30) – and of diagnostic and therapeutic procedures. Reasons for non-participation will also be studied.

In conclusion, the participation fulfills the assumptions for the power analyses underlying the dimensioning of the study and indicates so far that SCREESCO will be able to detect if there is a meaningful reduction in colorectal cancer incidence and mortality in long-term follow-up. Furthermore, the colonoscopy quality, the overall diagnostic yield and the low number of adverse events in a routine clinical setting, using certified endoscopists as standard of care, indicates that the SCREESCO design can be transferred to a population-screening service. It is of interest for future studies and screening design to follow the possible consequences of study arm-, gender- and anatomical location-specific adenoma detection rates. Upcoming SCREESCO analyses will examine colorectal cancer incidence and colonoscopy exposure in the control group and in non-attenders. Analyses of the primary outcome will be carried out according to a pre-specified statistical analysis plan after 10 and 15 years of follow-up.

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Data sharing statement regarding SCREESCO baseline report *Lancet Gastroenterology and Hepatology.*

For data sharing questions, please contact study PI Rolf.Hultcrantz@ki.se. The study protocol and statistical analysis plan are available on request and are also filed with Lancet Gastroenterology and Hepatology. De-identified individual participant data that underlie the results reported in this article (text, tables, figures, and appendices), can be available to researchers after application to the SCREESCO Steering Committee. Researchers have to provide a methodologically sound proposal for a project that conforms with the Swedish Ethical Review Authority permit for the project. Researchers will have to sign a data access agreement. Data will be made available at a secure remote server to achieve the aims in the approved proposal. They will be available from 3 months after publication and ending three years after article publication. Proposals regarding the data underlying this article may be submitted up to two years after publication. The SCREESCO study will not carry the costs of external projects.

Declaration of interest

All the authors declare no competing interests.

Contribution of authors statement

Conceptualisation of the SCREESCO study: RH, LH, AE

Study design: RH, AF, LH, AE, CM, RS

Funding: RH, CL

Project administration: AF, RH, LH, CL, MW

Scientific supervision of the project: all authors

Data collection: RH, AF, MW, CL, AP

Data analysis: AF, MW, RH, LH, AE

Visualisation of data: AF, MW

Data interpretation: AF, MW, LH, AE, RH, CM, RS with critical review from all the other authors

Writing original draft: AF, RH, MW, LH, AE

Writing – critical review and editing: all authors

Literature search: AF, LH, MW

RH, AF, MW and LH had full access to the data in the study and take responsibility for the integrity of the data.

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