Single CT colonography versus three rounds of faecal immunochemical test for population-based screening of colorectal cancer (SAVE): a randomised controlled trial

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Summary

Background Colorectal cancer screening is recommended for people aged 50–75 years, but the optimal screening test and strategy are not established. We aimed to compare single CT colonography versus three faecal immunochemical test (FIT) rounds for population-based screening of colorectal cancer.

Methods This randomised controlled trial was done in Florence, Italy. Adults aged 54–65 years, never screened for colorectal cancer, were randomly assigned (1:2) by simple randomisation and invited by post to either a single CT colonography (CT colonography group) or three FIT rounds (FIT group; each round was done 2 years apart). Exclusion criteria included previous colorectal cancer, advanced adenoma, or inflammatory bowel disease, colonoscopy within the last 5 years or FIT within the last 2 years, and severe medical conditions. Participants who had a colonic mass or at least one polyp of 6 mm or more in diameter in the CT colonography group and those who had at least 20 µg haemoglobin per g faeces in the FIT group were referred for work-up optical colonoscopy. The primary outcome was detection rate for advanced neoplasia. Outcomes were assessed in the modified intention-to-screen and per-protocol populations. The trial is registered with ClinicalTrials.gov, NCT01651624.

Findings From Dec 12, 2012, to March 5, 2018, 14 981 adults were randomised and invited to screening interventions. 5242 (35·0%) individuals (2809 [53·6%] women and 2433 [46·4%] men) were assigned to the CT colonography group and 9739 (65·0%) individuals (5208 [53·5%] women and 4531 [46·5%] men) were assigned to the FIT group. Participation in the screening intervention was lower in the CT colonography group (1286 [26·7%] of the 4825 eligible invitees) than it was for the FIT group (6027 [64·9%] of the 9288 eligible invitees took part in at least one screening round, 4573 [49·2%] in at least two rounds, and 3105 [33·4%] in all three rounds). The detection rate for advanced neoplasia of CT colonography was significantly lower than the detection rate after three FIT rounds (1·4% [95% CI 1·1–1·8] *vs* 2·0% [1·7–2·3]; p=0·0094) in the modified intention-to-screen analysis, but the detection rate was significantly higher in the CT colonography group than in the FIT group (5·2% [95% CI 4·1–6·6] *vs* 3·1% [2·7–3·6]; p=0·0002]) in the per-protocol analysis. Referral rate to work-up optical colonoscopy (the secondary outcome of the trial) was significantly lower for the CT colonography group than for the FIT group after three FIT rounds (2·7% [95% CI 2·2–3·1] *vs* 7·5% [7·0–8·1]; p<0·0001) in the modified intention-to-screen analysis, whereas no significant difference was observed in the per-protocol analysis (10·0% [8·4–11·8] vs 11·6% [10·8–12·4]). No major complications were observed in the CT colonography group after screening and work-up optical colonoscopy, whereas three cases of bleeding were reported in the FIT group after work-up optical colonoscopy (two after the first FIT and one after the second FIT).

Interpretation Greater participation makes FIT more efficient than single CT colonography for detection of advanced neoplasia in population screening for colorectal cancer. Nonetheless, higher detection rate in participants and fewer work-up colonoscopies are possible advantages of CT colonography as a screening tool, which might deserve consideration in future trials.

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For the Italian translation of the abstract see Online for appendix 1

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Introduction

Colorectal cancer is the fourth most commonly diagnosed malignancy worldwide and the second highest cause of death due to cancer.[1] Screening can detect early-stage colorectal cancer and its precursor, the adenomatous polyp, and it is strongly recommended for adults aged 50–75 years by the US Preventive Services Task Force,[2] the American Cancer Society,[3] and the European Council.[4] Several tests have been proposed and variably validated for colorectal cancer screening, including faecal immunochemical test (FIT), high-sensitivity guaiac-based faecal occult blood test, stool DNA test, colon capsule endoscopy, CT colonography, flexible sigmoidoscopy, and optical colonoscopy.[2–5] However, each test has advantages

Research in context

Evidence before this study

We searched PubMed for articles published between the inception of the database and Jan 7, 2022, using the search terms "(CT colonography) AND (faecal immunochemical test) AND (colonoscopy) AND (flexible sigmoidoscopy) AND (colorectal cancer screening)". No language restrictions were applied. No studies comparing CT colonography and repeated faecal immunochemical test were identified, but three studies evaluated the participation rate and yield of screening using CT colonography versus colonoscopy (two studies) and sigmoidoscopy (one study) in a population at average risk of colorectal cancer with an age ranging between 50 years and 75 years. Participation ranged from 18–34% for CT colonography, 27% for sigmoidoscopy, and 16–22% for colonoscopy. Detection rate for advanced neoplasia was 5·1–8·7% for CT colonography, 4·7% for sigmoidoscopy, and 8·7% for colonoscopy.

Added value of this study

Our study enhances our knowledge of colorectal cancer screening with CT colonography compared with faecal immunochemical test, which is the standard screening tool used in Florence, Italy. This study is the first to compare single CT colonography and repeated (three biennial) faecal immunochemical test screening rounds. Our study confirms the higher detection rate for colorectal cancer and advanced adenoma of CT colonography compared with a single faecal immunochemical screening test. However, CT colonography has an overall significantly lower detection rate for advanced neoplasia per invitee than three FIT rounds. This result can be explained by considering the key role of participation, which was consistently higher in each FIT round than in CT colonography.

The implications of all the available evidence

Our study suggests that the faecal immunochemical test remains the preferable screening tool for population screening, but also highlights that CT colonography could be used for opportunistic screening.

and disadvantages, and the optimal screening test and strategy for colorectal cancer screening are still under debate.

Although optical colonoscopy is the most accurate diagnostic test for colorectal cancer and enables removal of the adenomatous polyp, it has low patient attendance rates due to a variable combination of psychological, socioeconomic, and cultural factors,[6] and it is associated with a 0·06–0·07% risk of major complications, such as bleeding and perforations,[7,8] which hinders its use as a screening test.

FIT is an easy, home-feasible test, with participation rates of 47–50% in organised screening programmes.[9,10] It has been used for population screening in many European countries and has been shown to reduce incidence and mortality from colorectal cancer.[11,12] However, the sensitivity of FIT for detecting advanced neoplasia is low (approximately 14–35%),[13] and to be effective FIT has to be repeated every 2 years.[14] Additionally, FIT determines a high number of work-up optical colonoscopies following a positive test.[8]

CT colonography is a minimally invasive, low-radiation examination of the whole colon that is well tolerated.[15] CT colonography has been reported to have a higher participation rate and a lower number of bleeding and perforation complications than optical colonoscopy.[16,17] It has a high sensitivity for detecting colorectal cancer (96%) and large adenomas (90%),[18–20] and it has shown a detection rate for advanced neoplasia similar to optical colonoscopy in an observational study[21] and in a randomised trial.[22] Although the optimal schedule of CT colonography as a screening test has not been established, a 5 year interval has been suggested.[2,3] Furthermore, the specificity of CT colonography appears to be higher than FIT with a lower number of induced work-up optical colonoscopies.[17]

In Italy, population screening for colorectal cancer is done by FIT every 2 years, inviting all members of the resident population aged 50–70 years to participate. We hypothesised that offering CT colonography could provide equal or better detection of colorectal advanced neoplasia than repeated FIT rounds. Because the suggested rescreening interval of CT colonography is 5 years,[2,3] we aimed to compare the detection rate for advanced neoplasia by CT colonography with three FIT rounds, which require approximately the same time to be completed (4 years). The trial originally included a small group of participants who were screened with optical colonoscopy, but data on this cohort are not reported here. Results of the CT colonography, the first FIT round, and optical colonoscopy have been reported previously.[17]

Methods

Study design and participants

The SAVE study was a randomised controlled trial done in a one district of Florence, Italy. Adults aged 54–65 years who had never been invited to the FIT-based organised screening programme for colorectal cancer, used in Florence since 2000, were eligible for inclusion. Exclusion criteria were ascertained during a telephone or face-to-face consultation after people had been randomly assigned to an intervention group. Potential participants who had already received a diagnosis of colorectal cancer, advanced adenoma, or inflammatory bowel disease; who had had a optical colonoscopy in the

previous 5 years; who had had a FIT in the previous 2 years outside the screening programme; and those with severe medical conditions (eg, other advanced cancers, congestive heart failure, chronic renal insufficiency, and chronic respiratory disease) were excluded.

The study was approved by the Ethics Committee of the Local Health Unit of Florence, Florence, Italy (number 432/2010) and written informed consent was obtained by all participants. The study protocol has been published.[23]

Randomisation and masking

Information from potential participant's was extracted from the registries of Florence municipality and they were randomly assigned (1:2) to receive either a single CT colonography (CT colonography group) or three rounds of FIT (FIT group). Simple randomisation was done before invitation (LV) using computer random number generation, forcing the allocation of married people to the same group. For CT colonography screening, individuals were randomly assigned (1:1) to receive either CT colonography with reduced cathartic preparation or CT colonography with full cathartic preparation. The two subgroups were combined in the present study, as established a priori.[23] Invitees and investigators were not masked to study group allocation.

Procedures

Invitation to one of the two screening interventions was done by post with letters accompanied by a brochure providing information on the study aims and colorectal cancer screening features. Non-responders received a reminder by post.

Individuals invited to the CT colonography group were requested to contact the screening centre by telephone or email to organise an appointment for a face-to-face consultation with a nurse in which they were assessed for exclusion criteria and informed about the study, the screening examination, and the bowel preparation. After the consultation participants were scheduled for CT colonography.

Bowel preparation for CT colonography consisted of three doses of macrogol 3350 13·8 g dissolved in 150 mL of water per day for 3 days before the examination (reduced cathartic preparation) or with a solution of macrogol 3350 100 g and sodium ascorbate 4·7 g dissolved in 2 L of water administered in split-dose the day before and on the day of the examination (full cathartic preparation). Moreover, a 3-day low fibre diet was recommended.

Between 2 h and 3 h before CT colonography, 70 mL of iodinated oral contrast agent (sodium amidotrizoate and meglumine amidotrizoate) for tagging of faecal residue was administered. Before scanning, the colon was distended with an automatic CO_2 insufflator, after intravenous administration of 20 mg of hyoscine butylbromide if not contraindicated. CT colonographies were done in two hospitals in the same district of Florence with 64-slice and 128-slice CT scanners (Somatom Sensation 64 and Definition AS 128, Siemens, Erlangen, Germany) using a low radiation dose protocol (120 kVp; 50 effective mAs) and then transmitted to a centralised reading facility. All CT colonographies were interpreted by one of two radiologists who had reviewed more than 300 CT colonography examinations (LS and MF) who, after judgement about the adequacy of the examination, used computer-aided diagnosis (CAD) with a first-reader double reading approach (ie, the radiologist first reviewed CAD prompts and then evaluated the CT images without assistance).[24] Detection of a colonic mass or at least one polyp of 6 mm or more in diameter qualified the CT colonography test as positive and the participant was referred for a work-up optical colonoscopy. The type and number of extra-colonic findings have been previously reported.[17]

Participants randomly assigned to the FIT group were invited by post to complete the home-based test every 2 years. Individuals with possible exclusion criteria were asked to contact the screening centre, by telephone, for an additional assessment. They were requested to collect the FIT kit in any pharmacy of their district in Florence and to return faecal specimens to specific collection points within the district. FIT was processed with a fully automated immunochemical analyser and the positivity threshold was set at 20 µg haemoglobin per g faeces, which is the value used in the Italian FIT screening programme.[9] All participants with a positive FIT were invited to have a work-up optical colonoscopy. As per standard practice, participants who tested positive after FIT who declined work-up colonoscopy or had an incomplete work-up colonoscopy were referred to CT colonography. Participants who tested negative after FIT were invited to the subsequent FIT round.

All work-up optical colonoscopies after positive CT colonography or FIT were done by the same endoscopist (BM), who had completed more than 1000 screening colonoscopies per year for 5 years, under deep sedation with propofol, unless refused by the participant. Work-up optical colonoscopies were done within 1 month of positive CT colonography or FIT (according to the recommendations of the European Colorectal Cancer Screening Guidelines).[25]

One of two experienced gastrointestinal pathologists who had completed 2500 colonic histopathology reports evaluated colorectal lesions, which were classified as hyperplastic polyp, serrated, tubular, tubulo-villous or villous adenoma, or adenocarcinoma.[26] Advanced adenoma was defined as any adenoma more than 9 mm in diameter or with a villous histological component higher than 20%, or with severe dysplasia.[27] Sessile serrated adenomas per se were not analysed. Advanced neoplasia included two categories—cancer and advanced adenoma—which were defined as previously described.[27]

Outcomes

The primary outcome of this study was the detection rate for advanced neoplasia. The detection rate was assessed in the modified intention-to-screen population and the per-protocol population. In the FIT group, participants attending at least one of three screening rounds were considered for the per-protocol analysis. When assessing the detection rate in the modified intention-to-screen population, we considered the number of participants with screen-detected advanced neoplasia as the numerator with the total number of eligible invitees as the denominator (ie, randomly assigned individuals minus individuals with undelivered invitation letters and those who met exclusion criteria) rather than the number of randomly assigned individuals as the denominator. In the per-protocol analysis, the detection rate was defined as the proportion of participants with screen-detected advanced neoplasia divided by the total number of the participants screened.

The secondary outcome, established previously,[23] was the referral rate to work-up optical colonoscopy. It was defined as the proportion of participants screened who, after testing positive, were invited to have a work-up optical colonoscopy divided by the total number of eligible invitees in the modified intention-to-screen population and participants screened in the per-protocol population. In an additional prespecified assessment we compared the positive predictive value in the two groups for advanced neoplasia, defined as the number of true positive tests divided by the number of true positive plus false positive tests. A participant was considered to be a true positive following confirmatory optical colonoscopy and histopathology (gold standard assessment), whereas false positive participants tested negative after work-up optical colonoscopy.

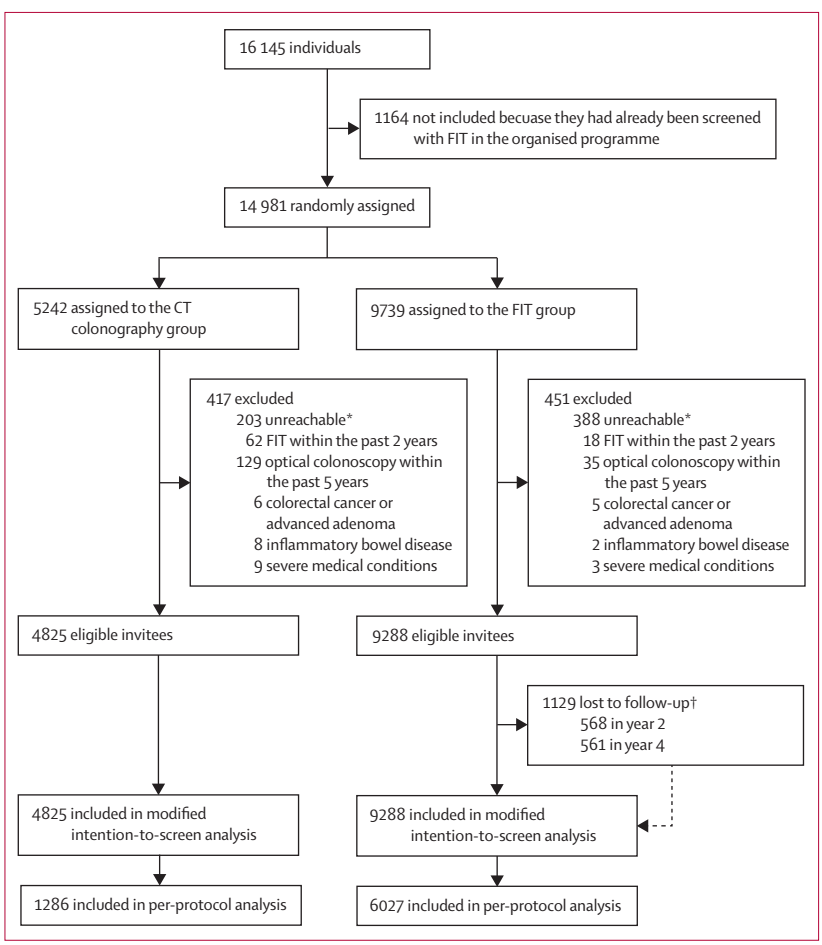

Figure 1: **Trial profile**
FIT=faecal immunochemical test. *Participants with undelivered invitation letters. †Participants lost to follow-up due to intervening change of address or unreachable.

Statistical analysis

Assuming a participation rate of 50% for each FIT round and 35% for CT colonography,[9,22] we calculated that we would be able to detect a statistically significant (α=0·05; power 0·80) difference of 1% in the detection rate for advanced neoplasia in the per-protocol analysis between a single round of CT colonography and three rounds of FIT with a sample size of 13 000 individuals (5000 in the CT colonography group and 8000 in the FIT group). In the modified intention-to-screen analysis, the adopted sample size would allow to detect as statistically significant a difference in the detection rate for advanced neoplasia lower than 1%.

Sample size calculations for the secondary outcome were reported in the study protocol.[23]

In a post-hoc analysis, detection rates for cancer, advanced adenoma, and advanced neoplasia stratified by sex and age groups were calculated for CT colonography and for each of the three FIT rounds. We also compared the detection rates for advanced adenomas at least 10 mm in diameter, adenomas, and hyperplastic polyps between the two groups.

In a post-hoc analysis, we determined and compared the number of optical colonoscopies after a positive CT colonography or FIT needed to diagnose one case of advanced neoplasia.

Finally, major complications of CT colonography and work-up optical colonoscopy, defined as bleeding or perforation, were collected at the time of the procedure and 1 month after the examination through a postal questionnaire sent to all participants in the CT colonography group and to the participants of the FIT group who underwent work-up colonoscopy.

The Pearson χ^2 test was used to compare detection rates, referral rates to work-up optical colonoscopy, and positive predictive values between the two groups. CIs for proportions were calculated using the normal approximation (Wald interval).

Two-sided p values of less than 0·05 were deemed statistically significant. The distribution for socio-economic status was determined as previously reported.[17] Statistical analyses were done using STATA (version 12.0). The trial is registered with ClinicalTrials.gov, NCT01651624.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 12, 2012, and March 5, 2018, 14 981 individuals were randomly assigned to the screening interventions (figure 1) and invited to participate in the study. 5242 (35·0%) participants (2809 [53·6%] women and 2433 [46·4%] men) were assigned to the CT colonography group and 9739 (65·0%) participants (5983 [61·4%] women and 3756 [38·6%] men) were assigned to the FIT group (table 1). Mean age was 59·0 years (SD 3·6) in both groups. Most participants belonged to the low and average socioeconomic tertiles. 203 (3·9%) individuals assigned to the CT colonography group and 388 (4·0%) to the FIT group were unreachable. 214 (4·1%) of 5242 individuals in the CT colonography group and 63 (0·65%) of 9739 individuals in the FIT group were excluded before intervention.

In the CT colonography group, 1286 (26·7%) of the 4825 eligible invitees completed screening. The positivity rate of CT colonography was 10·0% (129 of 1286 participants). Participation rate for work-up colonoscopy after positive CT colonography was 98·0% (126 of 129 participants). 20 (1·6%) of 1286 CT colonographies were deemed inadequate due to poor colonic distension or insufficient faecal tagging.

In the FIT group, 6027 (64·9%) of the 9288 eligible invitees participated in at least one screening round, 4573 (49·2%) in at least two rounds, and 3105 (33·4%) in all three rounds. The participation rates were 50·4% (4677 of 9288 individuals) for the first round of FIT, 54·2% (4723 of 8720 individuals) for the second round, and 52·8% (4305 of 8159 individuals) for the third round. Positivity rates were 5·5% (257 of 4677 participants) for the first round of FIT, 4·8% (228 of 4723 participants) for the second round, and 5·0% (215 of 4305 participants) for the third round.

In the FIT group, participation rates to work-up colonoscopy after a positive test were 84·4% (217 of 257 participants) for the first round, 82·5% (188 of 228 participants) for the second round, and 79·1% (170 of 215 participants) for the third round. All FIT tests were adequate. Detailed data concerning the participation rate and work-up optical colonoscopy for CT colonography and each FIT round are reported in appendix 2 (pp 1–2).

See Online for appendix 2

In the CT colonography group, 60 participants were diagnosed with advanced adenoma and seven were diagnosed with cancer on histology after work-up optical colonoscopy. In the FIT group, 164 participants were diagnosed with advanced adenoma and 22 were diagnosed with cancer on histology after work-up optical colonoscopy. In the modified intention-to-screen analysis, the detection rate for advanced neoplasia in the CT colonography group was significantly lower than in the FIT group after three rounds (1·4% [95% CI 1·1–1·8] *vs* 2·0% [1·7–2·3]; p=0·0094; table 2; figure 2). In the per-protocol analysis, the detection rate for advanced neoplasia in the CT colonography group was significantly higher than in the FIT group after three rounds, including individuals who attended at least one round of FIT round (5·2% [4·1–6·6] *vs* 3·1% [2·7–3·6]; p=0·0002; table 2; figure 2). Similar

	CT colonography group (n=5242)	FIT group (n=9739)
Age range		
54–60 years	3232 (61·7%)	5983 (61·4%)
61–65 years	2010 (38·3%)	3756 (38·6%)
Sex		
Female	2809 (53·6%)	5208 (53·5%)
Male	2433 (46·4%)	4531 (46·5%)
Socioeconomic status*		
Low	2316/5071 (45·7%)	4503/9437 (47·7%)
Average	1537/5071 (30·3%)	2621/9437 (27·8%)
High	1218/5071 (24·0%)	2313/9437 (24·5%)

Data are n (%). FIT=faecal immunochemical test. *Due to missing values, the total number of individuals included in the analyses per socioeconomic status does not always add up to the total number of individuals randomly assigned to each group

Table 1: **Sociodemographic characteristics**

	CT colonography group	FIT group	p value
Modified intention-to-screen analysis			
Number of eligible invitees*	4825	9288	..
Advanced neoplasia	67 (1·4%; 1·1–1·8)	186 (2·0%; 1·7–2·3)	0·0094
Cancer	7 (0·1%; 0·1–0·3)	22 (0·2%; 0·1–0·4)	0·25
Advanced adenoma	60 (1·2%; 1·0–1·6)	164 (1·8%; 1·5–2·1)	0·019
Advanced adenoma ≥10 mm in diameter	34 (0·7%; 0·4–0·9)	99 (1·1%; 0·9–1·3)	0·035
Adenoma	21 (0·4%; 0·3–0·7)	61 (0·7%; 0·5–0·8)	0·10
Hyperplastic polyp	16 (0·3%; 0·2–0·5)	19 (0·2%; 0·1–0·3)	0·15
Per-protocol analysis			
Number of participants screened†	1286	6027	..
Advanced neoplasia	67 (5·2%; 4·1–6·6)	186 (3·1%; 2·7–3·6)	0·0002
Cancer	7 (0·5%; 0·2–1·1)	22 (0·4%; 0·2–0·6)	0·35
Advanced adenoma	60 (4·7%; 3·5–5·9)	164 (2·7%; 2·3–3·2)	0·0002
Advanced adenoma ≥10 mm in diameter	34 (2·6%; 1·8–3·7)	99 (1·6%; 1·3–2·0)	0·015
Adenoma	21 (1·6%; 1·0–2·5)	61 (1·0%; 0·8–1·3)	0·055
Hyperplastic polyp	16 (1·2%; 0·7–2·0)	19 (0·3%; 0·2–0·5)	<0·0001

Data are n (%; 95% CI). FIT=faecal immunochemical test. *Randomly assigned individuals after exclusion of those unreachable and those meeting exclusion criteria. †For the FIT group the number of participants screened is the number of participants who attended at least one of the three rounds.

Table 2: **Detection rates of colorectal lesions according to the modified intention-to-screen and per-protocol analyses**

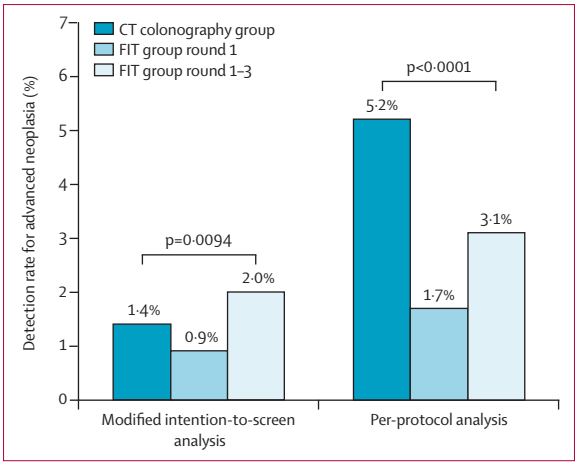

Figure 2: **Advanced neoplasia detection rates in the modified intention-to-screen and per-protocol analysis**
FIT 1–3 included individuals who attended at least one FIT round. FIT=faecal immunochemical test.

	CT colonography group	FIT group	p value
Referral rate in the modified intention-to-screen analysis			
Number of eligible invitees	4825	9288	..
Number referred to colonoscopy	129 (2·7%; 2·2–3·1)	700 (7·5%; 7·0–8·1)	<0·0001
Referral rate in the per-protocol analysis			
Number of participants*	1286	6027	..
Number referred to colonoscopy	129 (10·0%; 8·4–11·8)	700 (11·6%; 10·8–12·4)	0·10
Positive predictive value			
True positives plus false positives	126	575	..
Advanced neoplasia, true positives	67 (53·1%; 44·1–62·1)	186 (32·3%; 28·5–36·3)	<0·0001
Cancer, true positives	7 (5·6%; 2·2–11·1)	22 (3·8%; 2·4–5·7)	0·38
Advanced adenoma, true positives	60 (47·6%; 38·6–56·7)	164 (28·5%; 24·9–32·4)	<0·0001
Advanced adenoma ≥10 mm in diameter, true positives	34 (27·0%; 9·5–35·6)	99 (17·2%; 14·2–20·6)	0·27
Adenoma, true positives	21 (16·7%; 10·6–24·3)	62 (10·7%; 8·2–13·4)	0·0064

Data are n or n (%; 95% CI). FIT=faecal immunochemical test. *For the FIT group the number of participants is the number of individuals who attended at least one of the three FIT rounds.

Table 3: **Referral rate to work-up colonoscopy and positive predictive value**

significant differences were observed when the categories of advanced adenomas overall and of advanced adenomas at least 10 mm in diameter were considered (table 2). The detection rates stratified per sex and age groups were higher in men older than 60 years (appendix 2 p 3).

After the screening intervention, in the per-protocol analysis there was no significant difference (p=0·10) between the proportion of participants in the CT colonography (129 [10·0%] of 1286) and the FIT group (700 [11·6%] of 6027) who tested positive and were referred to work-up optical colonoscopy (table 3). In the modified intention-to-screen analysis, the referral rate to work-up optical colonoscopy in the CT colonography group was significantly lower (p<0·0001) than that in the FIT group after three rounds (table 3). The positive predictive value for advanced neoplasia in the CT colonography group was significantly higher (p<0·0001) than that in the FIT group after three rounds (table 3). The number of optical colonoscopies needed to diagnose one case of advanced neoplasia was 1·9 (126 work-up colonoscopies for 67 advanced neoplasia cases) in the CT colonography group and 3·1 (575 work-up colonoscopies for 186 advanced neoplasia cases) in the FIT group after three rounds (appendix 2 p 2).

No major complications were observed in the CT colonography group after screening and work-up optical colonoscopy, whereas three cases of bleeding were reported in the FIT group after work-up optical colonoscopy (two after the first FIT and one after the second FIT).

Discussion

In our randomised trial the results of the primary outcome suggest that a single CT colonography has a significantly lower detection rate for advanced neoplasia per invitee in the modified intention-to-screen-analysis but a higher detection rate per participant in the per-protocol analysis than three rounds of FIT in a population-based colorectal cancer screening setting. The opposing results of the modified intention-to-screen and per-protocol analyses are remarkable; however, they can be explained by considering the key role of participation, which was significantly higher for FIT than for CT colonography, and justifies the overall increased pick-up of advanced neoplasia.

The attendance to CT colonography in our study (26·7%) was lower than in a previous study done in the Netherlands (34%).[22] However, the detection rate per-participant of CT colonography in our study (5·2%) is in line with those of two randomised trials, one from the Netherlands (6·1%)[22] and one from Italy (5·1%),[28] and of an observational screening study in the US (3·2%).[21] Attendance to FIT screening in our study was in line with current data. 64·9% of our eligible invitees had at least one FIT round, a figure consistent with the participation observed in a Norwegian trial assessing three rounds FIT screening (68% for at least one FIT round).[8] The detection rate per-participant of FIT in our study (appendix 2 p 2) were slightly higher than the average detection rates in Italian FIT screening programme (1·1% after the first round and 0·8% after repeated rounds).[9]

Overall, comparison of the modified intention-to-screen and per-protocol analyses results for detection of advanced neoplasia in our study and other studies

supports the view that high participation in FIT is a distinctive advantage over CT colonography and is probably crucial to explain why this test is used for colorectal cancer screening.[9]

Possible reasons for the lower participation in the CT colonography group than in the FIT group are the required additional face-to-face visit for the CT colonography group and a number of other factors, including fear of radiation, reluctance to complete the 3-day cathartic preparation, and the invasiveness of CT colonography compared with FIT.[6] Stool based methods of population-based colorectal cancer screening have been established in Florence since 2000. Efforts to reduce the amount and duration of preparation for CT colonography could increase participation and acceptability of this screening intervention.[15,17] All of these factors, especially the lower awareness of CT colonography as a valuable colorectal cancer screening tool, might have biased our modified intention-to-screen results.

Nevertheless, three rounds of FIT were superior at detecting advanced neoplasia compared with one CT colonography. A similar feature was observed in a Norwegian colorectal cancer screening trial, which compared FIT with flexible sigmoidoscopy.[8]

Our per-protocol analysis revealed that the detection rates for advanced neoplasia and advanced adenoma in the CT colonography group was 1·5-times higher than for participants in the FIT group after at least one round. These data confirm the higher sensitivity of CT colonography compared with a single FIT.[17]

For the interpretation of CT colonography, we used a CAD system with a first-reader double reading approach for the polyp search. Such an approach, in which the CAD system is used to do the initial polyp search, is believed to be beneficial for reading high volume image data with a very low prevalence of disease, as seen in a screening setting. However, the detection rate of CT colonography using this approach can be influenced by the performance of the CAD algorithm.

The results of the secondary outcome of our study clearly favoured single CT colonography over three rounds of FIT. CT colonography induced a lower number of work-up optical colonoscopies per participant (2·7% in the CT colonography *vs* 7·5% in the FIT group). This result was obtained with a conservative threshold for FIT positivity (20 µg haemoglobin per g faeces). The threshold used for FIT leads to variation in the positivity rates for FIT. For instance, in the Dutch colorectal cancer screening programme positivity rate for FIT decreased from 10·6% to 6·7% after the threshold was increased from 15 to 47 µg haemoglobin per g faeces.[29]

This might have relevant implications in the context of population-based colorectal cancer screening because a lower threshold for FIT can enhance referral to work-up optical colonoscopy and restricted access to endoscopy can hinder performance of screening interventions.[8] Although the risk of complications of FIT are negligible and those of CT colonography are distinctly low, the overall risk of complications for both methods has to include the risk associated with work-up optical colonoscopy.

Despite the work-up optical colonoscopy procedure being the same for both groups, participant attendance for optical colonoscopy in the CT colonography group (98%) was higher than that in the FIT group (78–84%). A participant in whom a colonic lesion was detected via CT colonography might be more willing to undergo work-up colonoscopy than a participant who only had a positive FIT test.

Our results do not justify use of CT colonography as a screening test for colorectal cancer in a population setting due to the low attendance. However, higher detection rate and positive predictive value for advanced neoplasia per-participant justify the use of CT colonography as a screening test on an opportunistic basis, particularly when there is no organised FIT-based screening programme, providing that the patient is adequately informed about test characteristics, benefits, and risks, as recommended by the American Cancer Society, US Preventive Services Task Force, the European Society of Gastrointestinal and Abdominal Radiology, and the European Society of Gastrointestinal Endoscopy.[2,3,30] Comparative cost-effective analyses of CT colonography and repeated FIT, which were beyond the scope of our investigation, might justify reassessment of the role of CT colonography in population screening.

We recognise the following four limitations of our study. First, in the FIT programme used in Florence, invitations for participation stop once individuals reach 70 years of age. Accordingly, people older than 65 years were not included in the study because they would not have received the three scheduled FIT screening invitations. This age limitation might restrict the generalisability of our results. Second, we are aware that our per-protocol analysis could underestimate the detection rate for advanced neoplasia of individuals who participated in all three FIT rounds. However, the study protocol included an invitation to participate in subsequent FIT rounds for all eligible invitees and not only of those who participated in the first or second FIT rounds. Third, no strategy for quality assurance of CT colonography was applied. Finally, we did not include a group of participants directly invited to screening optical colonoscopy for the comparison of the detection rates. However, the low participation rate to optical colonoscopy in population-based screening is well known.[17,22]

In conclusion, the higher participation rate makes repeated FIT a more effective test for population screening of colorectal cancer compared with a single CT colonography. Relative advantages of CT colonography, which might justify its use for opportunistic screening, include higher detection rate in participating individuals and reduced numbers of work-up optical colonoscopy.

Contributors

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LS, MZ, and GG designed the study. LS, LV, MM, MF, FC and BM acquired, analysed, and interpreted the data. LS and MM drafted the manuscript. LV and MZ did the statistical analyses. SM and MM obtained funding. PM and GG coordinated administrative, technical, and material support. MZ supervised the study.

Declaration of interests

We declare no competing interests.

Data sharing

Deidentified participant data are available upon request for submission of research proposal to p.mantellini@ispro.toscana.it.

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