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ORIGINAL ARTICLE

Comparing CT colonography and flexible sigmoidoscopy: a randomised trial within a population-based screening programme

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ABSTRACT

Importance and aims The role of CT colonography (CTC) as a colorectal cancer (CRC) screening test is uncertain. The aim of our trial was to compare participation and detection rate (DR) with sigmoidoscopy (flexible sigmoidoscopy (FS)) and CTC in a screening setting.

Design setting and participants We conducted two randomised clinical trials (RCTs). (1) Participation RCT: individuals, aged 58 years, living in Turin (Italy), were randomly assigned to be invited to FS or CTC screening; (2) detection RCT: residents in northern Italy, aged 58–60, giving their consent to recruitment, were randomly allocated to CTC or FS. Polyps ≥6 mm at CTC, or 'high-risk' distal lesions at FS, were referred for colonoscopy (TC).

Main outcome measures Participation rate (proportion of invitees examined); DR of advanced adenomas or CRC (advanced neoplasia (AN)).

Results Participation was 30.4% (298/980) for CTC and 27.4% (267/976) for FS (relative risk (RR) 1.1; 95% CI 0.98 to 1.29). Among men, participation was higher with CTC than with FS (34.1% vs 26.5%, p=0.011). In the detection RCT, 2673 subjects had FS and 2595 had CTC: the AN DR was 4.8% (127/2673, including 9 CRCs) with FS and 5.1% (133/2595, including 10 CRCs) with CTC (RR 1.08; 95% CI 0.85 to 1.37). Distal AN DR was 3.9% (109/2673) with FS and 2.9% (76/2595) with CTC (RR 0.72; 95% CI 0.54 to 0.96); proximal AN DR was 1.2% (34/2595) for FS vs 2.7% (69/2595) for CTC (RR 2.06; 95% CI 1.37 to 3.10).

Conclusions and relevance Participation and DR for FS and CTC were comparable. AN DR was twice as high in the proximal colon and lower in the distal colon with CTC than with FS. Men were more likely to participate in CTC screening.

Trial registration number NCT01739608; Pre-results.

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BACKGROUND

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second cause of death from cancer worldwide.[1]

Significance of this study

What is already known on this subject?

- Sigmoidoscopy has been shown to reduce colorectal cancer (CRC) incidence and mortality in population-based randomised trials.
- CT colonography (CTC) has been proposed as a potential test for population-based screening due to its high acceptability and ability to image the entire colon.
- Comparative data of CTC performance in a screening setting are available only from a Dutch trial, using colonoscopy (TC) as a comparator test, and showing that the higher participation rate achievable with CTC may compensate the lower detection rate of advanced neoplasia compared with TC.

What are the new findings

- CTC and flexible sigmoidoscopy (FS), when used as primary screening tests in a population-based setting, show a comparable performance, both in terms of participation and of advanced neoplasia yield.
- Sigmoidoscopy appeared to compensate the expected lower diagnostic yield in the proximal colon with a higher detection rate in the distal part.
- Participation was higher among men invited for CTC screening than among those invited for FS screening, while no difference could be observed among women.

How might it impact on clinical practice in the foreseeable future?

- CTC shows equivalent diagnostic performance and acceptability as endoscopic tests. Comparative cost-effectiveness data are needed to assess the possible role of CTC in a screening setting, also considering the impact of different management strategies for extra-colonic findings.

Once-only flexible sigmoidoscopy (FS) reduces CRC incidence and mortality, especially in the distal colon.[2–5] Thus, its use as a primary screening test is recommended, and FS-based organised population programmes are ongoing.[6]

Head-to-head screening studies with colonoscopy have shown that CT colonography (CTC) is a marginally invasive imaging test that accurately detects advanced neoplasia (AN).[7–10] In a randomised setting, CTC showed a higher participation rate than colonoscopy and a similar diagnostic yield for AN.[11] Similarly to FS, CTC does not require sedation and cathartic preparation.[12 13] In addition, CTC systematically explores the proximal colon, which is beyond reach of FS. Computer-aided detection (CAD) when using a first-reader paradigm may further enhance the capabilities of CTC by reducing its reporting time while ensuring high diagnostic accuracy.[14–16]

No direct comparison between CTC and FS is available to date. To bridge this knowledge gap we have undertaken a study aimed at comparing AN detection rate (DR) and participation rate of non-cathartic CTC and FS in average risk individuals aged 58–60 years in the context of a population-based screening programme.

METHODS

Study design and participants

The study design and rationale have been described in detail in a previous publication and are available online.[14] To reduce a possible source of bias, related to self-selection of subjects at different baseline risk for CRC to different screening protocols, this study included two separate randomised clinical trials (RCTs): (1) a pragmatic RCT (proteus 1) comparing participation among eligible people living in Turin, who were randomly allocated to be invited for CRC screening by CTC or FS; (2) an efficacy RCT (proteus 2) comparing detection of AN (advanced adenoma+CRC) of CTC and FS among volunteers, conducted in all sites. The two RCTs differed in their recruiting and randomisation procedures.

The target population included 58 year old residents in the Piedmont Region (three screening centres involved with six clinical sites) and 60 year old residents of the city of Verona (two clinical sites involved), eligible for invitation in their respective population-based screening programmes between October 2010 and December 2013. General practitioners (GPs) were asked to exclude individuals if they had a family (more than one first-degree relative) or personal history of CRC/polyps; if they had a history of IBD; if they had undergone colonoscopy in the previous 5 years or a faecal occult blood test (FOBT) in the previous 2 years; those diagnosed with a terminal illness.

Approval of the study was obtained by the local ethics review committees of all participating clinical sites. All individuals gave informed written consent. Screening-related assessments were offered free of charge to all subjects attending the invitation.

Randomisation and invitation procedures

For both the RCTs, the randomisation scheme was computer generated within the information technology screening system which also manages screening invitations and appointments as described elsewhere.[14]

Participation trial: proteus 1

All individuals eligible for invitation in Turin in September 2012 and in January 2013 were randomly allocated (ratio: 1:1) to FS or CTC. Subjects were mailed a personal letter, signed by their GP, offering a pre-fixed appointment to one of the tests, based on the outcome of randomisation. The letter included a leaflet that concisely described the screening procedure and its possible side effects. Subjects were asked to call the screening centre to confirm, modify, or cancel their appointment. A reminder letter was mailed to all subjects who did not respond to the initial invitation within 45 days.

Detection trial: proteus 2

Eligible individuals from Piedmont and Verona screening programmes were sent an invitation letter to participate in the trial. The letter included a leaflet that outlined the trial objectives, described the screening tests, their advantages and possible risks. The mailing specified that participation in the trial entailed the consent to be randomised to receive one of the two screening tests. If interested, invitees were asked to call the screening centre to give their consent to be recruited. Responders giving their consent to enter the study were randomly allocated either to FS or CTC and offered the appointment for the assigned test. Individuals refusing randomisation and non-responders were invited after 1 month to FS according to the regional screening protocol.

Screening procedures

Flexible sigmoidoscopy

Bowel preparation consisted of a single enema (133 mL of 22% sodium phosphate) self-administered at home 2 h before the test. A standard scope was advanced beyond the sigmoid-descending colon junction without sedation. Polyps <10 mm detected during FS were immediately removed and sent for histologic evaluation. Subjects with polyps ≥10 mm, or with 'high risk' polyps (at least one advanced adenoma <10 mm, or more than two small tubular adenomas with low-grade dysplasia) were referred for colonoscopy (see section 'Assessment colonoscopy'); those with polyps too large to be removed or with suspected CRCs were referred for surgery; those with a negative FS or with low-risk polyps were discharged. Screenees were invited to repeat the test at a later date if preparation was inadequate.

CT colonography

Non-cathartic CTC preparation and exam technique are described in detail elsewhere[14] (see also online supplementary appendix). Briefly, screenees were instructed to follow a low-residue diet and to intake a sachet of stool softener at the three main meals starting 3 days before the examination date. Faecal tagging was obtained by oral administration of an iodine solution starting 2 h before the examination. Following automatic insufflation of carbon dioxide, supine and prone scans were obtained using a low-dose scanning protocol. Intravenous contrast medium was not administered; n-butyl-scopolamine was administered according to the common practice in each participating centre. Radiographers and nurses participating in the study followed a one-day course on exam technique and quality assurance.

In Piedmont, CTC exams were transferred through a regional ICT network to a centralised reading centre for interpretation. In Verona, CTC interpretation was performed in the two local hospitals participating in the study. CTC data were interpreted on a commercial workstation (CAD-COLON software V.1.20, im3D, Turin, Italy),[14] using a previously validated CAD reading paradigm.[14–16] CAD reading consisted of the evaluation of the list of CAD prompts, followed by a fast two-dimensional review (see also online supplementary appendix). Participants with inadequate CTC because of poor bowel preparation, poor

distension or artefacts were invited by telephone to undergo FS. Participants with lesions ≥6 mm were contacted by phone to arrange colonoscopy. Participants with negative results (no colonic lesions or polyps <6 mm) were informed by regular mail. Extra-colonic findings (ECFs) were assessed using a standard soft-tissue window. Cases with E4 findings, according to C-RAD classification,[17] or with aortic aneurysms ≥4 cm were invited to undergo additional testing. ECFs known prior to CTC were excluded from further assessments (see also online supplementary appendix).

All radiologists participating in the trial had reported at least 300 colonoscopy-verified CTC examinations; in addition they were required to attend a 3-day hands-on CTC screening course and to obtain a per-patient sensitivity and specificity of at least 90% during a final examination, which consists of interpreting 30 screening cases. Radiographers and nurses attended a course aimed to introduce and explain the study procedures, and to discuss specific requirements related to the examination procedures, or patient's counselling, within the study. No formal assessment was planned at the end of the training.

Assessment colonoscopy

Colonoscopy was performed using standard high-definition endoscopes following a cathartic bowel preparation.[14] The exam was considered complete if the caecum was visualised or, in the case of failure, when a subsequent colonoscopy, performed within 6 months after the index one, reached the caecum; the combined results of the two exams were considered for analysis. All detected lesions were measured with open biopsy forceps and annotated according to size, morphology and localisation.

Histology was defined according to WHO criteria.[18] Advanced adenoma was defined as an adenoma with any of the following features: size of at least 10 mm, high-grade dysplasia, or villous component >20%. Cancer was defined as the invasion of malignant cells beyond the muscularis mucosae.

Adverse events of screening tests

Adverse events of CTC, FS and colonoscopy were recorded at the time of procedures. All participants were instructed to contact the primary investigator if adverse events occurred within 2 weeks of the procedures.

Statistical analysis

Primary outcomes were participation rate to the screening invitation and DR for AN (ie, CRC and advanced adenomas). Participation rate was defined as the number of participants undergoing the screening test relative to the total number of invitees. The DR for AN was defined as the proportion of participants with AN over the total number of participants. Differences were expressed as relative risk with 95% CIs. Multivariable estimation of prevalence ratios were obtained using log-binomial regression; adjustments were made for age, gender, family history (one first-degree relative with CRC) and screening programme, to allow for variability in adenoma and CRC DRs. We also estimated the prevalence of advanced neoplasms by colonic location (rectum-sigmoid colon vs proximal colon, from descending colon to caecum) in the two arms. All statistical tests were two sided and were considered statistically significant at $p<0.05$.

The SAS statistical software (V.9.1) was used for the analysis.

Sample size

Assuming 25% participation in FS screening,[6 19] 1000 invitees per group would allow 80% power to detect as statistically significant an absolute increase in CTC participation rate >5%, with a 0.05 significance level. The overall AN prevalence at FS was assumed to be 5%.[6 19] Assuming a similar increase in the AN yield with CTC as with TC,[19] a sample size of 2500 participants per group could allow 80% power to be achieved to detect as statistically significant the expected 2% absolute increase in AN prevalence between screening groups, with a 0.05 significance level for the two-sided test.

RESULTS

Participation trial: proteus 1

The flow diagram on the left in figure 1 summarises the results of the participation trial. The overall participation rate was 30.4% (298/980) for CTC and 27.0% (264/976) for FS (RR 1.12; 95% CI 0.98 to 1.29). Participation rates for CTC and FS did not differ among women (26.7% vs 27.6%; RR 0.98; 95% CI 0.79 to 1.20), while men showed a higher participation to CTC screening (34.1% vs 26.5%; RR 1.3; 95% CI 1.07 to 1.65; p=0.011).

Detection trial: proteus 2

The trial flow for AN detection is also described in figure 1. The final analysis included 2673 subjects allocated to the FS and 2595 to the CTC group (table 1).

The screening examination was judged inadequate in 79 (3.0%) cases in the CTC group and in 65 (2.4%) in the FS group. The reasons for non-diagnostic CTC were inadequate faecal tagging in 69% (55/79) of cases, poor bowel preparation in 23% (18/79) and insufficient distension in 8% (6/79); poor bowel preparation was mentioned as the reason for non-diagnostic exam in all cases in the FS arm. Among the 271 participants (10.1%) referred to colonoscopy in the FS group, compliance to colonoscopy was 87% (235/271) and the caecum was reached in 96% of cases (225/235); in the CTC group, 264 (10.2%) were referred for colonoscopy; 260 (99%) performed the exam with a completion rate of 94% (n=244).

The AN DR was 5.1% (n=133, including 10 CRCs) in the CTC arm compared with 4.7% (n=127, including 9 CRCs) in the FS arm (RR 1.1; 95% CI 0.9 to 1.4; p=0.524). Per-patient DR, by gender and size of the most advanced lesion, is reported in table 2. Male gender emerged as an independent predictor of AN risk in the multivariable analysis, also adjusted for screening arm and trial centre (table 3).

The distribution of AN detected by the two tests showed a different pattern by colonic site (table 4). The prevalence of AN in the distal colon was 4.1% (109) for FS versus 2.9% (76) for CTC (RR 0.72; 95% CI 0.54 to 0.96), while the prevalence of AN in the proximal colon was 2.7% (69) for CTC vs 1.3% (34) for FS (RR 2.06; 95% CI 1.37 to 3.10). Isolated AN in the proximal colon was present in 57 (2.2%) and 18 (0.7%) CTC and FS participants, respectively. In the CTC group, men were at higher risk of having proximal advanced disease than women (CTC: RR 2.1; 95% CI 1.3 to 3.2).

Histology of detected adenomas according to size is reported in table 5. Out of 560 adenomas detected among FS participants, 117 (20.8%) were at least 10 mm in size, 93 (16.6%) had a villous component >20% and 42 (7.5%) contained high-grade dysplasia. Out of 408 adenomas detected among CTC participants, 129 (31.6%) were at least 10 mm in size, 110 (30%) had a villous component >20% and 37 (9.1%) contained high-grade dysplasia. Advanced and non-advanced FS adenomas were mostly sessile and left sided; CTC non-advanced adenomas were mostly sessile and right sided, whereas CTC advanced adenomas were sessile or pedunculated and almost equally

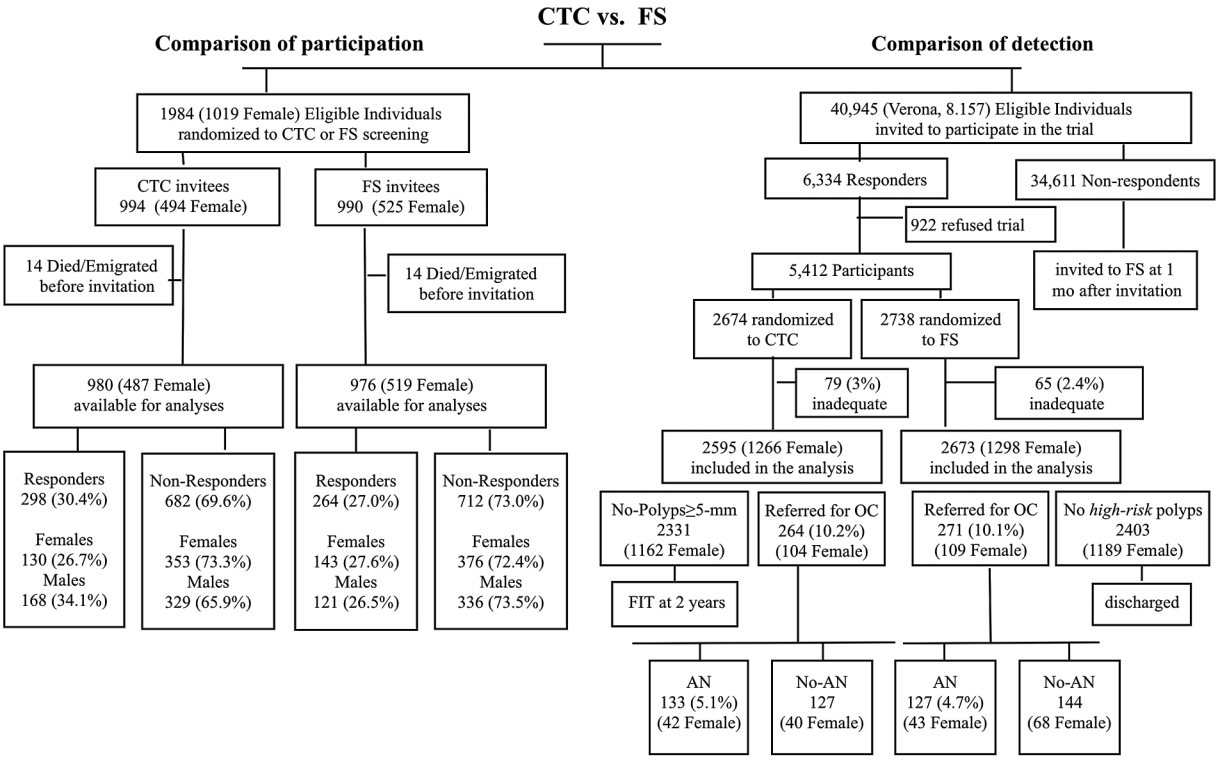

Figure 1 Flow diagram of the two randomized clinical trials (RCTs) comparing participation and advanced neoplasia detection of CT colonography (CTC) and flexible sigmoidoscopy (FS).

distributed in the left and right colon. Additional information on polyp morphology and distribution is available in the online supplementary appendix (table S1).

ECFs and adverse events

Clinically relevant ECFs (CT colonography reporting and data system (C-RADS) E4 and aortic aneurysms ≥4 cm) were diagnosed in 35 (1.2%) CTC participants, of whom 29 (1.0%) had a new diagnosis that required further assessment. Further details on ECFs are provided in the online supplementary appendix.

In the CTC group, 14 (0.5%) patients complained of a vago-vagal reaction and one (0.04%) a cutaneous rash. In the FS group, vago-vagal reactions occurred in 9 (0.4%) patients. In both groups, adverse events resolved spontaneously and did not require medical treatment or hospital admission.

Table 1 Detection trial: patient characteristics

	Sigmoidoscopy	CT colonography	Total
Age (years)			
Mean (SD)	58.6 (1.08)	58.6 (1.09)	58.6 (1.08)
Gender, N (%)			
Male	1375 (51.4)	1329 (51.2)	2704 (51.3)
Female	1298 (48.6)	1266 (48.8)	2564 (48.7)
Family risk*, N (%)			
No	2444 (92.1)	2309 (90.9)	4753 (86.0)
Yes	209 (7.9)	230 (9.1)	439 (8.5)
Previous colonoscopy†, N (%)			
No	2324 (94.1)	2266 (91.6)	4590 (87.2)
Yes	344 (12.9)	328 (12.6)	672 (12,8)

*Information was missing in 56 CTC cases and in 20 FS cases.
†Information was missing in 1 CTC case and in 5 FS cases.
FS, flexible sigmoidoscopy.

DISCUSSION

According to this study, the performance of CTC and FS when used as primary screening tests in a population-based setting is comparable, both in terms of participation and AN detection.

Equivalent participation rates could be related to the similar perceived burden of the two tests, in that both do not necessitate sedation and cathartic preparation. Contrary to what was expected, the offer of a less-invasive radiologic examination apparently did not enhance participation. However, even if the study was not powered to detect such difference as statistically significant, a 3.4% absolute increase in screening uptake may result in a substantial additional impact of the programme at the population level. Of note, adherence to FS screening in our study was similar to the average attendance in the local screening programme,[6 19] suggesting that the population enrolled in this study is representative of the population complying with the screening invitation. The COCOS trial[11] showed a higher CTC uptake, but participation rate in CRC screening trials with FS and FIT in The Netherlands is also higher, suggesting a greater awareness of cancer prevention in the Dutch population.[11 20]

The finding of a differential uptake by gender with the two tests deserves consideration. Reports from the Piedmont screening program[6 19] consistently showed higher participation in FS screening among men than among women whereas no such trend was observed in this study. A 30% increase in screening uptake was instead observed among men invited for CTC compared with those invited for FS. A higher screening uptake among men may enhance the health impact of screening, since men have a higher AN prevalence compared with women. However, measures to reduce the gender gap in screening coverage also need to be implemented when using CTC, as is already the case with FS.[19]

The lack of superiority of CTC compared with FS in terms of AN detection was at least in part unexpected. Similar to

Table 2 Per-patient findings by gender for sigmoidoscopy and CT colonography (CTC)

	Flexible sigmoidoscopy			CTC			
	Women N=1298 % (95% CI)	Men N=1375 % (95% CI)	Total N=2673 % (95% CI)	Women N=1266 % (95% CI)	Men N=1329 % (95% CI)	Total N=2595 % (95% CI)	RR* (95% CI)
No finding	1087 83.8 (81.6 to 85.7)	1018 74.0 (71.6 to 76.3)	2105 78.8 (77.1 to 80.3)	1183 93.4 (91.8 to 94.7)	1183 89.0 (87.2 to 90.6)	2366 91.2 (90.0 to 92.2)	–
Non-neoplastic polyp†	82 6.3 (5.5 to 7.8)	143 10.4 (8.8 to 12.1)	225 8.4 (7.4 to 9.5)	12 0.9 (0.5 to 1.6)	12 0.9 (0.5 to 1.6)	24 0.9 (5.9 to 1.4)	**0.42** **(0.36 to 0.48)**
Non-advanced adenoma	86 6.6 (5.3 to 8.1)	130 9.5 (8.0 to 11.1)	216 8.1 (7.0 to 9.2)	29 2.3 (1.9 to 3.3)	43 3.2 (2.4 to 4.3)	72 2.8 (2.0 to 3.5)	**0.76** **(0.65 to 0.89)**
Advanced adenoma of any size	41 3.2 (2.3 to 4.3)	77 5.6 (4.4 to 6.9)	118 4.4 (3.7 to 5.3)	37 2.9 (2.0 to 4.0)	86 6.5 (5.2 to 7.9)	123 4.7 (4.0 to 5.6)	**1.07** **(0.84 to 1.37)**
Advanced adenoma <6 mm	6 0.46 (0.2 to 1.0)	6 0.44 (0.2 to 0.9)	12 0.45 (0.2 to 0.8)	0 0.0 (0.0 to 0.3)	3 0.23 (0.05 to 0.7)	3 0.12 (0.02 to 0.3)	–
Advanced adenoma 6–9 mm	4 0.31 (0.08 to 0.8)	6 0.44 (0.2 to 0.9)	10 0.37 (0.02 to 0.68)	7 0.55 (0.20 to 1.00)	15 1.1 (0.6 to 1.8)	22 0.9 (0.5 to 1.3)	–
Advanced adenoma ≥6 mm	35 2.4 (1.6 to 3.4)	70 4.7 (3.6 to 5.9)	105 3.6 (2.9 to 4.3)	37 2.4 (1.6 to 3.4)	83 5.1 (4.0 to 6.4)	120 3.8 (3.8 to 4.6)	**1.17** **(0.91 to 1.52)**
Advanced adenoma ≥10 mm	31 2.4 (1.6 to 3.4)	64 4.7 (3.6 to 5.9)	95 3.6 (2.9 to 4.3)	30 2.4 (1.6 to 3.4)	68 5.1 (4.0 to 6.4)	98 3.8 (3.8 to 4.6)	**1.06** **(0.81 to 1.40)**
Colorectal cancer§	2 0.2 (0.02 to 0.6)	7 0.5 (0.02 to 1.00)	9 0.3 (0.02 to 0.6)	5 0.4 (0.1 to 0.9)	5 0.4 (0.1 to 0.9)	10 0.4 (0.2 to 0.7)	**1.14** **(0.47 to 2.31)**

*Crude RR (relative risk), experimental (CTC) versus control (FS) group.
†Normal, hyperplastic or inflammatory.
§FS arm—UICC stage I, n=3; II, n=2; III, n=3; IV, n=1.
CTC arm—UICC stage I, n=3; II, n=5; III, n=2.
FS, flexible sigmoidoscopy; UICC, Union for International Cancer Control.

colonoscopy, CTC has the advantage of a systematic assessment of the proximal colon. Indeed, the DR of CTC for proximal AN was twofold higher than with FS. The finding of a similar prevalence of proximal AN at CTC as at colonoscopy screening in a comparable target population enrolled in the SCORE 3 trial[19] would suggest that colonoscopy and CTC may have comparable sensitivity in detecting proximal AN. Of note, about 80% of subjects with proximal AN (including three CRCs) did not have 'high-risk' distal lesions and they would not have been diagnosed with FS screening.

Table 3 Factors associated with advanced neoplasia detection at multivariate analysis

	RR*	95% CI
Gender		
Women	1	
Men	1.94	1.50 to 2.51
1 FDR with colorectal cancer		
No	1	
Yes	1.30	0.87 to 1.95
Performed previous TC		
No	1	
Yes	0.61	0.39 to 0.96
Screening test		
Sigmoidoscopy	1	
CT colonography	1.05	0.84 to 1.35

*RR adjusted for screening centre and for all other variables in the model.
FDR, first-degree relative; RR, relative risk; TC, colonoscopy.

In contrast with previous comparative studies, the DR of distal AN was substantially lower with CTC than with FS.[7 8 11] There could be several contributing factors for this that warrant further investigation. First, the non-cathartic preparation scheme and the tagging regimen adopted in this study might have affected exam quality, particularly of the distal colon. Second, the distal colon is more rigid than the proximal colon and is the favoured site of diverticular disease, and this may result in a suboptimal distension when insufflating CO_2. Third, particularly in the above reported adverse conditions, adopting a new reading algorithm with CAD as the first reader might have negatively affected CTC interpretation. Being a highly technological test and a newcomer, CTC has the potential to improve its performances.

Two additional variables of CTC must be considered in the setting of population-based screening programmes, namely ECFs and radiation exposure. The adoption of strict criteria to refer people with ECFs to clinical assessments in our study resulted in a very low rate of referrals. Still, in programmes targeting asymptomatic subjects, in the absence of strong evidence supporting the effectiveness of assessing and treating ECFs, the choices concerning ECF management may have a critical impact on the cost-effectiveness profile of the test.

Table 4 Distribution of recto-sigmoid and proximal advanced neoplasia among flexible sigmoidoscopy (FS) and CT colonography (CTC) screenees

	Sigmoidoscopy, N % (95% CI)	CTC, N % (95% CI)	RR* (95% CI)
Distal colon			
Women (1298 FS; 1266 CTC)	36 2.8 (1.9 to 3.8)	23 1.8 (1.2 to 2.7)	0.66 (0.40 to 1.10)
Men (1375 FS; 1329 CTC)	73 5.3 (4.3 to 6.6)	53 4.0 (3.0 to 5.2)	0.76 (0.53 to 1.08)
Total	109 4.1 (3.3 to 4.9)	76 2.9 (2.3 to 3.7)	0.72 (0.54 to 0.96)
Proximal colon†			
Women (1298 FS; 1266 CTC)	13 1.0 (0.5 to 1.7)	21 1.7 (1.0 to 2.5)	1.66 (0.83 to 3.27)
Men (1375 FS; 1329 CTC)	21 1.5 (0.9 to 2.3)	48 3.6 (2.7 to 4.8)	2.3 (1.4 to 3.8)
Total	**34‡ 1.3 (0.9 to 1.8)**	**69‡ 2.7 (2.1 to 3.4)**	**2.06 (1.37 to 3.10)**

*Crude RR (relative risk), experimental (CTC) versus control (FS) group.
†Proximal is defined as descending colon, transverse colon, ascending colon, or caecum.
‡Including 16 (47.1%) FS and 12 (17.3%) CTC cases who had synchronous advanced neoplasia in the distal colon.

Similarly the possible impact of radiation exposure of a large number of asymptomatic subjects is unknown and potentially harmful, even when low-dose scanning protocols are applied.

In the detection trial we adopted a two-stage recruitment procedure to ensure comparability between screening arms, by reducing a potential source of variability related to self-selection of subjects with different baseline characteristics and CRC risk in the two arms. The finding of a higher participation rate among men (showing a higher AN prevalence) in the CTC arm in the participation trial would indicate that self-selection could indeed bias the estimate of the relative DR. Restricting enrolment to volunteers enhanced the validity of the comparison between the screening methods, although it could limit the generalisability of the study findings. However, a recent analysis[21] comparing subjects who volunteered in the SCORE trial, which targeted a similar population, with those who did not respond

Table 5 Histological characteristics of advanced neoplasia detected by CT colonography (CTC) and flexible sigmoidoscopy (FS) according to size

	Sigmoidoscopy, N (%; 95% CI)	CTC, N (%; 95% CI)	RR (95% CI)
Lesion size ≥10 mm, n	117	129	
TV or villous	54 (46.2; 36.9 to 55.6)	70 (54.3; 45.7 to 63.1)	1.2 (0.9 to 1.5)
High-grade dysplasia	26 (22.2; 15.1 to 30.6)	16 (12.4; 7.3 to 19.4)	
Tubular	56 (47.9; 38.5 to 57.3)	46 (35.7; 27.6 to 44.6)	0.8 (0.6 to 1.0)
High-grade dysplasia	4 (3.4; 0.9 to 8.5)	2 (1.6; 0.2 to 5.5)	
SSA/P—TSA	7 (5.1; 2.4 to 1.2)	13 (10.1; 5.5 to 16.6)	1.7 (0.9 to 4.1)
High-grade dysplasia	0 (0.0; 0.0 to 3.1)	2 (1.6; 0.2 to 5.5)	
Lesion size 6–9 mm, n	138	153	
TV or villous	19 (13.8; 8.5 to 20.7)	32 (20.9; 14.8 to 28.2)	1.5 (0.9 to 2.6)
High-grade dysplasia	1 (1.1; 0.02 to 4.0)	7 (4.6; 1.9 to 9.2)	
Tubular	113 (81.9; 74.4 to 87.9)	109 (71.2; 63.4 to 78.3)	0.9 (0.8 to 1.0)
High-grade dysplasia	1 (0.7; 0.02 to 4.0)	7 (4.6; 1.8 to 9.2)	
SSA/P—TSA	6 (4.3; 1.6 to 9.2)	12 (7.8; 4.2 to 13.3)	2.1 (0.8 to 5.5)
High-grade dysplasia	0 (0.0)	0 (0.0)	–
Lesions size ≤5 mm, n	305	126	
TV or villous	15 (4.9; 2.8 to 8.0)	8 (6.3; 2.8 to 12.1)	1.3 (0.6 to 3.0)
High-grade dysplasia	1 (0.4; 0 to 1.8)	2 (1.6; 0.2 to 5.6)	
Tubular	273 (89.5; 85.5 to 92.7)	107 (84.9; 77.5 to 90.7)	1.3 (0.8 to 2.3)
High-grade dysplasia	4 (1.3; 0.4 to 3.3)	3 (2.4; 0.5 to 6.8)	
SSA/P—TSA	17 (5.6)	11 (8.7)	1.6 (0.8 to 3.2)
High-grade dysplasia	0 (0.0)	0 (0.0)	
Overall	**560**	**408**	
Total number of advanced adenomas*	156 (27.9; 24.2 to 31.8)	179 (43.9; 39.0 to 48.8)	1.6 (1.3 to 1.9)
Total number of non-advanced lesions	404 (72.1; 68.2 to 75.8)	229 (56.1; 51.2 to 61.0)	

*Including serrated polyps ≥10 mm, or with high-grade dysplasia.
SSA/P, small sessile serrated adenoma/polyp; TSA, traditional serrated adenoma; TV, tubulovillous.

to the recruitment questionnaire showed that volunteers had lower CRC mortality, but the same CRC incidence as non-responders, suggesting that our enrolment procedure is unlikely to influence the main outcome of the trial. It should be considered that the effectiveness of the two approaches in population screening settings not only depends on the relative DR but it results from the combination of participation and DR, the former being more strictly influenced by local conditions.

In conclusion, in a population-based screening trial, CTC showed a similar AN detection and acceptability as FS. Comparative cost-effectiveness data are needed to assess the possible role of CTC in this setting.

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