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Diagnostic Accuracy of Computed Tomographic Colonography for the Detection of Advanced Neoplasia in Individuals at Increased Risk of Colorectal Cancer

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COLORECTAL CANCER (CRC) accounts for approximately 210 000 deaths each year in Europe.¹ The majority of CRCs arise within adenomatous polyps,² and polypectomy is associated with a reduction in CRC incidence and

For editorial comment see p 2498.

Context Computed tomographic (CT) colonography has been recognized as an alternative for colorectal cancer (CRC) screening in average-risk individuals, but less information is available on its performance in individuals at increased risk of CRC.

Objective To assess the accuracy of CT colonography in detecting advanced colorectal neoplasia in asymptomatic individuals at increased risk of CRC using unblinded colonoscopy as the reference standard.

Design, Setting, and Participants This was a multicenter, cross-sectional study. Individuals at increased risk of CRC due to either family history of advanced neoplasia in first-degree relatives, personal history of colorectal adenomas, or positive results from fecal occult blood tests (FOBTs) were recruited in 11 Italian centers and 1 Belgian center between December 2004 and May 2007. Each participant underwent CT colonography followed by colonoscopy on the same day.

Main Outcome Measures Sensitivity and specificity of CT colonography in detecting individuals with advanced neoplasia (ie, advanced adenoma or CRC) 6 mm or larger.

Results Of 1103 participants, 937 were included in the final analysis: 373 cases in the family-history group, 343 in the group with personal history of adenomas, and 221 in the FOBT-positive group. Overall, CT colonography identified 151 of 177 participants with advanced neoplasia 6 mm or larger (sensitivity, 85.3%; 95% confidence interval [CI], 79.0%-90.0%) and correctly classified results as negative for 667 of 760 participants without such lesions (specificity, 87.8%; 95% CI, 85.2%-90.0%). The positive and negative predictive values were 61.9% (95% CI, 55.4%-68.0%) and 96.3% (95% CI, 94.6%-97.5%), respectively; after group stratification, a significantly lower negative predictive value was found for the FOBT-positive group (84.9%; 95% CI, 76.2%-91.3%; $P < .001$).

Conclusions In a group of persons at increased risk for CRC, CT colonography compared with colonoscopy resulted in a negative predictive value of 96.3% overall. When limited to FOBT-positive persons, the negative predictive value was 84.9%.

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mortality.³ The target lesions in mass screening programs are advanced adenomas, which harbor the greatest cancer risk, and early stage CRC,⁴ but adherence to screening procedures remains suboptimal.^{5,6}

Computed tomographic (CT) colonography has been shown to be sufficiently accurate in detecting colorectal neoplasia.^{7,8} Less invasive and better tolerated than colonoscopy,^{9,10} CT colo-

nography is now considered a valid alternative for CRC screening in the general population.¹¹

Individuals with first-degree family history of advanced colorectal neoplasia, those who have had resection of co-

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lorectal adenomas, and those with positive results from fecal occult blood tests (FOBTs) are at increased risk of CRC. However, adherence to follow-up colonoscopy in these individuals is suboptimal.¹²⁻¹⁴ Being less invasive and thus more tolerable, CT colonography may increase acceptability and adherence to screening, but little information is available on its performance.

The aim of our study was to assess sensitivity and specificity of CT colonography in detecting advanced neoplasia (ie, advanced adenoma or CRC) 6 mm or larger in individuals at increased risk of developing CRC, because of either family history of advanced colorectal neoplasia in first-degree relatives, personal history of adenomas, or positive results from immunochemical FOBTs.

METHODS

Study Design and Population

In this multicenter cross-sectional study, each participant underwent CT colonography followed by colonoscopy on the same day. Both tests were carried out in the same center.

Individuals were eligible for inclusion into the study if they met 1 of 3 categories. Group 1 comprised first-degree relatives of patients with advanced colorectal neoplasia diagnosed before the age of 60 years and were aged 40 to 65 years (family-history group). Group 2 individuals entered a colonoscopy surveillance program after endoscopic removal of colorectal adenomas¹⁵ and were aged 18 to 70 years (postpolypectomy group). Group 3 comprised individuals with positive results from FOBTs who were aged 59 to 69 years and participating in a CRC screening program (FOBT-positive group).

Individuals were excluded if they had any of the following: clinical diagnosis of familial adenomatous polyposis or hereditary nonpolyposis CRC,¹⁶ normal colonoscopy or sigmoidoscopy performed within the last 3 years, diagnosis of cancer at any site at the time of selection, severe comorbidity limiting life expectancy, inflammatory bowel

disease, celiac disease, autoimmune disease, symptoms or signs that clinically warranted colon imaging, evidence of increased risk of being harmed by undergoing colonoscopy as judged by the endoscopist, psychological or physical conditions that contraindicated colonoscopy, anticoagulant therapy, or pregnancy at time of study inclusion or CT colonography.

Center Selection

Participating centers were required to have the following 4 facilities: a radiology unit equipped with at least one 4-slice CT scanner, where at least 1 radiologist had reported 50 or more CT colonography procedures under supervision of an expert; a digestive endoscopy unit with state-of-the-art video endoscopy and endoscopists who had performed at least 500 colonoscopies and 100 polypectomies; a general surgery unit; and a pathology unit with a pathologist experienced in evaluating colorectal diseases. The centers also needed the resources to perform at least 50 extra CT colonography procedures and 50 extra colonoscopies yearly in addition to their routine workloads. Following a start-up visit by investigators from the coordinating center, 21 centers (20 in Italy, 1 in Belgium) were approved to join the study; each center was required to enroll at least 1 participant per month. An institutional review board including all participating centers agreed on the study protocol, which was then approved by each center's ethical committee.

Participant Enrollment

Eligible participants were prospectively selected in each center by a study investigator in 3 ways. Relatives of patients with advanced neoplasia were recruited into the family-history group (group 1) after interviews with all patients referred for surgery or endoscopic polypectomy because of histologically proven advanced colorectal neoplasia diagnosed before the age of 60 years; their first-degree relatives aged 40 to 65 years were identified and permission obtained to contact them. Par-

ticipants were identified for groups 2 and 3 by interviewing all individuals without personal history of colorectal neoplasia who attended the gastroenterology units involved in the study and by periodically checking indications for colonoscopy reported in the endoscopy waiting list.

All eligible participants were contacted, interviewed, and offered participation in the study. Individuals who accepted were prospectively registered and booked for same-day and same-center CT colonography and colonoscopy. Written informed consent was obtained from each participant. A dedicated password-protected database was designed and managed on a secure server by the Clinical Trials Core Facility of the National Institute for Cancer Research, Genoa, Italy (<http://clinicaltrials.istge.it/ist/rde>).

CT Colonography Protocol

Full bowel purgation was required because participants had to undergo colonoscopy on the same day as CT colonography. No specific colon cleansing directions were given to the participating centers, but internationally recognized quality standards had to be met.¹⁷ Hydrosoluble iodine agents alone or in combination with barium sulfate were accepted for oral tagging.^{7,18}

Each participant was placed on a CT table and a small flexible rectal catheter was positioned. *N*-butyl-scopolamine was administered intravenously according to common practice in the participating centers. Immediately before scanning, pneumocolon was obtained through insufflation of room air or carbon dioxide; this was performed either manually using a balloon pump or with an automatic device until maximum tolerance was reached. Computed tomographic colonography was performed with the participant in the supine and prone positions with the following scanning protocol: 120 kilovolt peak (kVp), 50 or fewer effective mA per second, and a section thickness not greater than 2.5 mm. Intravenous contrast medium was not administered. Duration of CT colonography, reporting

time, and adverse events were recorded.

On completion of the CT scan, 1 radiologist interpreted the CT colonography on his or her own workstation using either 2-dimensional or 3-dimensional primary reading according to preference. Lesions were assigned to 1 of the following bowel segments: cecum, ascending colon including the hepatic flexure, transverse colon including the splenic flexure, descending colon, sigmoid colon, and rectum. Lesion size was reported as the measurement of its largest diameter (the stalk of the polyp when visible was not considered for measurement) on 2-dimensional reformatted images, using a standard window setting of 1500 Hounsfield units. The results of the CT colonography interpretation were recorded on different pages, one for each of the 6 bowel segments, and put separately into sealed envelopes that were delivered to the endoscopy unit where colonoscopy was scheduled. Because of the low specificity of CT colonography for small lesions, polyps smaller than 6 mm were recorded but not registered in the envelopes delivered to the endoscopy unit.¹⁹

Colonoscopy Protocol

Colonoscopy was performed at least 3 hours after CT colonography. Sedation was carried out according to the common clinical practice of each participating center.

The endoscope was advanced to the cecum and the entire length of the bowel was examined during endoscopy withdrawal. The endoscopist was initially blinded to the result of CT colonography; at the end of each bowel segment evaluation, CT colonography results for that segment were disclosed (segmental unblinding). If a polyp measuring 6 mm or larger was detected at CT colonography but not at colonoscopy, the segment was reexamined to resolve the discrepancy.²⁰ The duration of colonoscopy and any adverse events were recorded.

Radiologists and endoscopists were required to evaluate the adequacy of preparation for each segment of the

bowel. Global examination quality was considered optimal when distension and visualization of the bowel wall were excellent; good when part of the bowel wall was not visualized due to luminal collapse, fluid, or stool (however, still allowing detection of lesions ≥ 10 mm); and poor when examination quality could not guarantee visualization of large lesions.²¹ The main reasons for incomplete visualization (fecal and/or liquid residue or collapsed segment) were recorded.

Lesion Matching and Classification

According to the adopted segmental checking procedure, a lesion found at CT colonography was matched to a corresponding one found at colonoscopy when it was located in the same or adjacent colon segment and when its size differed by no more than 50%.⁷ Matching was performed immediately after conclusion of both tests, if necessary by reviewing colonoscopy video registration and CT colonography images. This algorithm was used only for the "per-polyp" analysis.

Lesion size was measured at endoscopy using open biopsy forceps. All visible lesions were removed; those retrieved were sent for local pathologist evaluation and classified according to criteria from the World Health Organization.²² Adenomas were considered advanced when 10 mm or larger, if they had a 20% or more villous component, or if they had high-grade dysplasia; all the others were considered low-risk adenomas.

Statistical Methods

The reference standard for lesion diagnosis was the result of the unblinded colonoscopy (ie, all polyps ≥ 6 mm detected at colonoscopy before and after segmental unblinding of CT colonography) and the histological evaluation of the removed polyps. Reasons for exclusion from the analyses were indicated in the research protocol as follows: cases entered by a center that enrolled fewer than 1 participant per month during the study period, participants who withdrew their consent

before testing or refused to undergo CT colonography or colonoscopy, incomplete colonoscopy with a negative test result up to the examined point, or histology of the largest lesion not being available. Participants with a complete CT colonography and a diagnostic colonoscopy, including those interrupted due to obstruction, were considered for analysis.

End Points. The primary end point of the study was CT colonography performance as a screening test using unblinded colonoscopy as the reference standard. The analysis was performed according to a per-patient evaluation.

Participants were considered as having a positive result at the reference standard when at least 1 advanced neoplasia 6 mm or larger was found at the reference standard. When 2 or more lesions were removed in the same patient, the one with the worst histology was classified as the index lesion; for multiple lesions with the same histology, the largest one was considered. Participants without colorectal lesions, those with nonadenomatous lesions, those with nonadvanced adenomas, and those with advanced adenomas smaller than 6 mm were classified as having negative results.

Computed tomographic colonography was reported to be positive when at least 1 lesion 6 mm or larger was detected; otherwise, it was reported as negative. If CT colonography was positive and the index lesion was an advanced neoplasia 6 mm or larger, the CT colonography result was considered to a true positive. If CT colonography was positive but the case was classified as negative at the reference standard, the CT colonography result was considered a false positive. Computed tomographic colonography sensitivity, specificity, positive predictive value, and negative predictive value, along with their relative 95% confidence intervals (CIs), were calculated cumulatively and according to study group.

Secondary End Points. Per-patient sensitivity, specificity, and positive and negative predictive values were calcu-

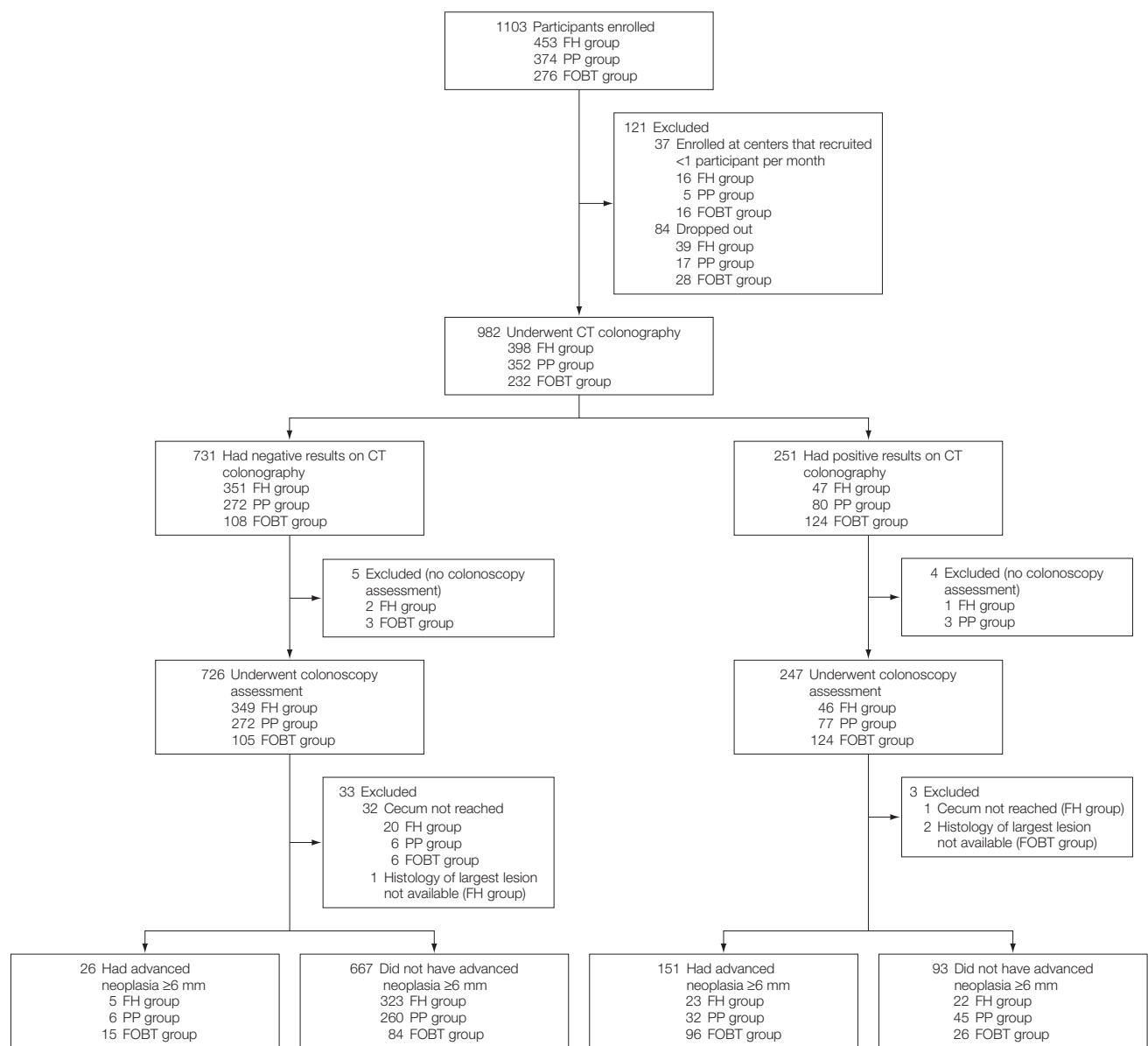
lated also for advanced neoplasia 10 mm or larger. For this purpose, if the CT colonography result was positive and the index lesion was an advanced neoplasia 10 mm or larger, the CT colonography result was considered a true positive for a lesion in that size class. If the CT colonography result was positive but no advanced neoplasia 10 mm or larger was found at unblinded colo-

noscopy, the CT colonography result was considered a false positive for a lesion in that size range. Per-polyp sensitivity was calculated as the percentage of positive CT colonography matching findings among all advanced neoplasia sized in the range of interest that were detected at unblinded colonoscopy, using the matching algorithm described before.

The χ^2 test was used to assess statistical significance of differences among proportions. All *P* values involved hypothesis tests against a 2-sided alternative and were considered significant when *P* < .05. The analyses were performed using SAS release 9.1 (SAS Institute, Cary, North Carolina).

Sample Size Estimate. We assumed that CT colonography could be pro-

Figure. Flow Diagram of Observational Cohort for Study of Diagnostic Accuracy of CT Colonography in Individuals at Increased Risk of Colorectal Cancer



CT indicates computed tomographic; FH, family history; PP, postpolypectomy; FOBT, fecal occult blood test-positive.

Table 1. Demographic Characteristics and Colorectal Findings of the Study Participants

	All (N = 937)	Study Group		
		Family-History (n = 373)	Postpolypectomy (n = 343)	FOBT-Positive (n = 221)
Age at enrollment, median (range), y	60.0 (30-70)	51.1 (40-65)	61.0 (30-70)	65.0 (59-70)
Sex, No. (%)				
Female	422 (45.0)	198 (53.1)	133 (38.8)	91 (41.2)
Male	515 (55.0)	175 (46.9)	210 (61.2)	130 (58.8)
Colorectal findings, No. (%)				
Negative for advanced neoplasia ≥ 6 mm	760 (81.1)	345 (92.5)	305 (88.9)	110 (49.8)
No lesion	521 (55.6)	259 (69.4)	207 (60.3)	55 (24.9)
Any histology ≤ 6 mm	184 (19.6)	71 (19.0)	69 (20.1)	44 (19.9)
Nonadenomatous lesion ^a	27 (2.9)	11 (3.0)	13 (3.8)	3 (1.4)
Low-risk adenoma	28 (3.0)	4 (1.1)	16 (4.7)	8 (3.6)
Positive for advanced neoplasia ≥ 6 mm	177 (18.9)	28 (7.5)	38 (11.1)	111 (50.2)
Advanced adenoma 6-9 mm	43 (4.6)	9 (2.4)	8 (2.3)	26 (11.8)
Advanced adenoma ≥ 10 mm	93 (9.9)	15 (4.0)	25 (7.3)	53 (24.0)
Carcinoma 6-9 mm	3 (0.3)	0	0	3 (1.4)
Carcinoma ≥ 10 mm	38 (4.1)	4 (1.1)	5 (1.5)	29 (13.1)

Abbreviation: FOBT, fecal occult blood test.

^aIn 27 cases, the index lesion was nonadenomatous: in 19, 1, and 7 cases, this was a hyperplastic polyp sized 6-9 mm, a hyperplastic polyp sized ≥ 10 mm, and normal colonic mucosa or other benign lesions ≥ 6 mm, respectively.

posed as a screening test if its sensitivity was 70% or greater. Assuming that 150 participants had advanced lesions found at colonoscopy, the precision of the estimates would be approximately $\pm 7\%$ for CT colonography sensitivity between 80% and 90%. Thus, under a conservative assumption that CT colonography sensitivity for advanced lesions was greater than 80%, the study had greater than 90% power of rejecting the hypothesis at .05 (1-sided level of significance) that CT colonography true sensitivity was 70% or less. The projected prevalence of advanced lesions in the study population ranged from 4% to 15% depending on the relative contribution of the 3 study groups. Accordingly, it was estimated that no fewer than 1000 participants would have had to be enrolled for the study to have sufficient statistical power and that recruitment had to be continued until 150 participants with advanced neoplasia had been found at unblinded colonoscopy.

RESULTS

Between December 2004 and May 2007, 1103 participants were enrolled in 17 centers. Recruitment varied between 1 and 291 participants per center. Of the enrolled participants, 937 participants

(85.0%) from 12 centers (11 in Italy, 1 in Belgium) were included in the analysis (FIGURE). Of those 937 participants, 373 (39.8%) were in the family-history group, 343 (36.6%) in the postpolypectomy group, and 221 (23.6%) in the FOBT-positive group; the prevalence of advanced neoplasia was 7.5%, 11.1%, and 50.2%, respectively ($P < .001$). Participant characteristics and size and histology of the colorectal findings are reported in TABLE 1.

Technical details of the CT colonography examination are in TABLE 2. There were no clinically significant complications after CT colonography. The median time spent by participants in the CT suite (available for 658 participants) was 15 minutes (range, 10-50 minutes). The median time required for interpretation of the CT colonography studies was 18 minutes (range, 3-55 minutes); time spent was shorter for primary 2-dimensional assessment (17 minutes; range, 3-55 minutes) than for primary 3-dimensional assessment (20 minutes; range, 5-55 minutes; $P < .001$).

Global examination quality was reported for 863 participants. It was optimal in 533 participants (61.8%), good in 282 (32.7%), and poor in 48 (5.6%).

Table 2. Technical Details of the Computed Tomographic Colonography Examinations

	Total, No. (%) (N = 937)
Fecal tagging	
Not administered	620 (66.2)
Administered	317 (33.8)
Computed tomographic scanner	
4-8 rows	109 (11.6)
16 rows	658 (70.3)
32-64 rows	170 (18.1)
Reconstruction interval	
0.6-1.0 mm	404 (43.1)
1.2-1.5 mm	533 (56.9)
Slice thickness	
1.00-1.25 mm	475 (50.7)
2.0-2.5 mm	462 (49.3)
Type of primary assessment	
2-Dimensional	697 (74.4)
3-Dimensional	240 (25.6)

The main reasons for poor-quality examinations were fecal residue in 33 participants (3.8%), liquid residue in 5 (0.6%), and bowel collapse in 5 (0.6%); the reason for poor global examination quality was not recorded in 5 cases (0.6%).

The CT colonography sensitivity, specificity, and positive and negative predictive values to detect a participant with at least 1 advanced neoplasia 6 mm or larger were 85.3% (95% CI,

Table 3. Per-Patient Analysis of Computed Tomographic Colonography in Detecting Advanced Neoplasia

Performance Measure	All	Study Group			P Value ^a
		Family-History	Postpolypectomy	FOBT-Positive	
Sensitivity, % (95% CI)	85.3 (79.0-90.0)	82.1 (62.4-93.2)	84.2 (68.1-93.4)	86.5 (78.4-92.0)	.58
No. of patients	177	28	38	111	
Specificity, % (95% CI)	87.8 (85.2-90.0)	93.6 (90.4-95.9)	85.3 (80.7-88.9)	76.4 (67.1-83.7)	
No. of patients	760	345	305	110	
Positive predictive value, % (95% CI)	61.9 (55.4-68.0)	51.1 (36.0-66.1)	41.6 (30.6-53.3)	78.7 (70.2-85.4)	<.001
No. of patients	244	45	77	122	
Negative predictive value, % (95% CI)	96.3 (94.6-97.5)	98.5 (96.5-99.5)	97.7 (95.2-99.2)	84.9 (76.2-91.3)	
No. of patients	693	328	266	99	

Abbreviations: CI, confidence interval; FOBT, fecal occult blood test.

^aAccording to the χ^2 test for differences among the 3 groups.**Table 4.** Analysis of False-Positive Results From Computed Tomographic Colonography

Reason for False-Positive Classification	All (760 Negative Cases)	Study Group		
		Family-History (345 Negative Cases)	Postpolypectomy (305 Negative Cases)	FOBT-Positive (110 Negative Cases)
Polyp ≥ 6 mm ^a	42 (5.5)	11 (3.2)	20 (6.6)	11 (10.0)
Polyp 4-5 mm ^b	10 (1.3)	2 (0.6)	4 (1.3)	4 (4.0)
Perception error ^c	17 (2.2)	4 (1.2)	5 (1.6)	8 (7.0)
Fecal residue	16 (2.1)	2 (0.6)	11 (3.6)	3 (3.0)
Spasm	2 (0.3)	0	2 (0.7)	0
Appendiceal stump	1 (0.1)	0	1 (0.3)	0
Fold	3 (0.4)	2 (0.6)	1 (0.3)	0
CT colonography image not available	2 (0.3)	1 (0.3)	1 (0.3)	0
Total	93 (12.2)	22 (6.4)	45 (14.8)	26 (23.6)

Abbreviations: CT, computed tomographic; FOBT, fecal occult blood test.

^aNonadenomatous lesion or low-risk adenoma with size ≥ 6 mm at endoscopic assessment.^bLesion of any histology sized 4-5 mm at endoscopic assessment with a diameter ≥ 6 mm at CT colonography.^cFinding that was not confirmed by retrospective review.

79.0%-90.0%), 87.8% (95% CI, 85.2%-90.0%), 61.9% (95% CI, 55.4%-68.0%), and 96.3% (95% CI, 94.6%-97.5%), respectively.

Considering only disease-positive participants with advanced neoplasia 10 mm or larger, CT colonography identified 119 of 131 participants with at least 1 such lesion (sensitivity, 90.8%; 95% CI, 84.2%-95.0%) and 681 of 806 participants without (specificity, 84.5%; 95% CI, 81.8%-86.9%); the corresponding positive and negative predictive values were 48.8% (95% CI, 42.3%-55.2%) and 98.3% (95% CI, 97.0%-99.1%), respectively. Sensitivity for participants with cancer was 95.1% (95% CI, 83.5%-99.4%); CT colonography detected 39 of 41 participants with cancer, including all 3 with diameters of 6

to 9 mm. The diagnostic performance of CT colonography in detecting participants with at least 1 advanced neoplasia 6 mm or larger according to the risk group is in TABLE 3. When comparing CT colonography performance in the 3 different groups of participants, sensitivity for advanced neoplasia 6 mm or larger was similar. On the other hand, specificity was significantly higher in the family-history and postpolypectomy groups as compared with the FOBT-positive group (93.6% and 85.3% vs 76.4%, respectively; $P < .001$).

Positive predictive value varied between 41.6% in the postpolypectomy group and 78.7% in the FOBT-positive group ($P < .001$), and the negative predictive value ranged between 84.9% in the FOBT-positive group and 98.5% in

the family-history group ($P < .001$). The test-positive rate in the family-history, postpolypectomy, and FOBT-positive groups was 12.1%, 22.4%, and 55.2%, respectively.

TABLE 4 lists results of the retrospective analysis performed by 2 experienced radiologists on the 93 cases that were negative at colonoscopy and classified as positive at CT colonography. The false-positive rate varied from 6.4% in the family-history group to 23.6% in the FOBT-positive group. The main reasons for erroneous CT interpretation were presence of nonadvanced neoplasia in polyps 6 mm or larger ($n = 42$; 5.5%) and perception errors ($n = 17$; 2.2%).

A total of 375 lesions 6 mm or larger were detected in 235 participants. Histology and size of the 347 endoscopically retrieved lesions are reported in TABLE 5 according to their bowel location. Sensitivity according to the per-polyp analysis is listed in TABLE 6. Blinded colonoscopy missed 2 advanced adenomas: a 13-mm pedunculated polyp in the cecum and an 18-mm flat lesion in the ascending colon. Two participants were hospitalized for bleeding after polypectomy.

COMMENT

The overall per-patient sensitivity for CT colonography detecting advanced neoplasia 6 mm or larger and 10 mm or larger was 85.3% and 90.8%, respectively, which are comparable with figures reported in 2 large trials on average-risk individuals^{7,8} but higher than

those of 2 previous multicenter studies that included patients with clinical indication for colonoscopy or those with family history of CRC.^{23,24} Computed tomographic colonography can only classify a lesion by its size. Thus, large hyperplastic polyps or large low-risk adenomas can generate false-positive findings on CT colonography when considering as positive only patients with advanced neoplasia 6 mm or larger, as we did in our study. This may lead to a possible reduction of CT colonography specificity. In our survey, the index lesion was a low-risk adenoma or a nonadenomatous lesion in 28 and 27 participants, respectively, thus accounting for only 5.9% of the participants. Therefore, our specificity was similar to that of other studies primarily aimed at detecting adenomas 6 mm or larger independently of their histology.^{7,8}

Computed tomographic colonography was performed safely: no serious adverse events were recorded. Furthermore, to minimize radiation-induced cancer risk, we adopted a low-dose protocol that did not negatively affect CT colonography performance.²⁵ Our study also provided the opportunity to assess CT colonography performance in 3 different groups of asymptomatic individuals at increased risk of carrying advanced colorectal neoplasia. This allowed us to draw important practical implications.

The prevalence of advanced neoplasia in our participants with family history of advanced colorectal neoplasia was 7.5%, which is similar to the figures reported elsewhere.^{12,26} Our values of a 12% test-positive rate, 51% positive predictive value, and 82% sensitivity suggest a potentially effective use of CT colonography as an alternative to colonoscopy for screening individuals with family history of advanced colorectal neoplasia. Computed tomographic colonography has been shown to be better accepted than colonoscopy²⁷ and has a negligible risk of serious adverse events; thus, it may help increase the low adherence reported for individuals who are candidates for

Table 5. Histology and Size of Lesions Detected on Reference Standard According to Location

Segment and Histological Type	Size		Total (n = 347)
	6-9 mm (n = 173)	≥10 mm (n = 174)	
Rectum			
Carcinoma	1	4	5
Advanced adenoma	14	20	34
Low-risk adenoma	7	0	7
Nonadenomatous lesion	9	1	10
Sigmoid colon			
Carcinoma	1	14	15
Advanced adenoma	18	51	69
Low-risk adenoma	23	0	23
Nonadenomatous lesion	10	6	16
Descending colon			
Carcinoma	0	5	5
Advanced adenoma	6	13	19
Low-risk adenoma	9	0	9
Nonadenomatous lesion	1	1	2
Transverse colon			
Carcinoma	0	7	7
Advanced adenoma	7	13	20
Low-risk adenoma	10	0	10
Nonadenomatous lesion	9	2	11
Ascending colon			
Carcinoma	1	8	9
Advanced adenoma	15	14	29
Low-risk adenoma	6	0	6
Nonadenomatous lesion	8	1	9
Cecum			
Carcinoma	0	3	3
Advanced adenoma	7	11	18
Low-risk adenoma	6	0	6
Nonadenomatous lesion	5	0	5
Total			
Carcinoma	3	41	44
Advanced adenoma	67	122	189
Low-risk adenoma	61	0	61
Nonadenomatous lesion	42	11	53

Table 6. Per-Polyp Analysis of the Sensitivity of CT Colonography for the Detection of Advanced Adenoma and Cancer^a

	Size		
	≥6 mm	≥10 mm	6-9 mm
Advanced adenoma			
Sensitivity, % (95% CI)	72.0 (65.0-78.2)	80.3 (72.2-87.0)	56.7 (44.0-68.8)
Detected lesions	136	98	38
No. of lesions	189	122	67
Carcinoma			
Sensitivity, % (95% CI)	95.5 (84.5-99.4)	95.1 (83.5-99.4)	100 (36.8-100)
Detected lesions	42 ^b	39 ^b	3
No. of lesions	44	41	3
All advanced lesions			
Sensitivity, % (95% CI)	76.4 (70.3-81.6)	84.1 (77.3-89.1)	58.6 (46.2-70.0)
Detected lesions	178	137	41
No. of lesions	233	163	70

Abbreviations: CI, confidence interval, CT, computed tomographic.

^aSensitivity for each size class was calculated as the proportion of matching lesions detected at CT colonography among those detected by the reference standard (see "Methods" for matching algorithm). Lesion size was determined according to the reference standard (comparison with open forceps).

^bCT colonography missed 2 carcinomas: a 30-mm protruding mass in the sigmoid and a 20-mm sessile lesion in the cecum.

screening,¹² which is the main negative factor affecting its efficacy in reducing mortality from CRC.

Surveillance colonoscopy following polypectomy accounts for approximately one-fourth of all endoscopic procedures,²⁸ but the yield in terms of polypectomy rate is very low despite this workload. In our postpolypectomy group, the prevalence of advanced neoplasia was 11%, in line with the available literature.²⁹ Lower figures are observed in patients without high-risk adenomas at the index colonoscopy, but our protocol did not stratify participants according to this information. According to our results, 16% of advanced adenomas developing during postpolypectomy follow-up would have not been detected by CT colonography. However, this negative aspect must be weighed against the higher dropout rate reported during colonoscopy follow-up of postpolypectomy patients.¹³ Here again, the better acceptance²⁷ and lower invasiveness of CT colonography might reduce this dropout rate, thus making it an effective test for increasing in absolute terms the protective effect of postpolypectomy follow-up toward the development of CRC. This strategy may be most useful in patients whose index lesion is a low-risk adenoma, thus reducing the workload of endoscopy units while still ensuring an efficient detection rate of clinically relevant lesions.

The prevalence of advanced colorectal neoplasia in our participants with positive FOBT results was 50%, which is also in line with the reported literature.³⁰ Despite this evidence, nonadherence to post-FOBT colonoscopy has been shown to occur in up to one-third of cases.¹⁴ This would obviously reduce the efficacy of mass screening using FOBT. Our results do not support using CT colonography as a first-line strategy in FOBT-positive subjects. Because of the high prevalence of advanced neoplasia in this group of participants, colonoscopy would have been performed in 55% of the cases if CT colonography had been used as a screening test, making such a strategy

not as cost-effective as using colonoscopy as a first-line screening test. This statement is also supported by the low specificity (76%) in our FOBT-positive participants, because of the higher rate of nonadenomatous lesions and low-risk adenomas detected at CT colonography and the high rate of observer errors in this group. Errors may be explained by radiologists not being blinded to the participant's group; the awareness of an expected high prevalence of disease in FOBT-positive participants might increase false-positive reporting, thus generating useless referral to colonoscopy. Nevertheless, the high accuracy of CT colonography for cancer in our study is a valid argument for its use in FOBT-positive patients who refuse colonoscopy.

There were 3 limitations to the study. The first limitation is that, because this was a multicenter study, CT colonography protocols and radiologist experience were probably not uniform across participating centers; it has not been assessed how results could have been affected by differences in colon preparation, scanning protocol, and interpretation paradigm. However, this study was designed while bearing in mind how CT colonography is typically performed in daily clinical practice. To further improve test performance, CT colonography technique should be standardized internationally and adequate training strategies implemented.

A second limitation of our study was the variable working conditions between centers and the variable motivations of the radiologist, and this limitation may have adversely affected CT colonography performance. Most radiology units have heavy clinical workloads, and our protocol imposed on the radiologist a 3-hour time limit for reporting CT colonography results to the endoscopy suite while still handling ongoing routine clinical work. Both of these stress factors create nonideal conditions in a screening setting. Furthermore, the time it took to interpret CT colonography results was lengthy and

might not be cost-effective in mass screening programs. Also, the prior knowledge that their reports would be checked against those of the subsequent colonoscopy findings might have caused radiologists to take more time in an effort to be more accurate. Computer-aided diagnosis and reporting in a protected environment might help increase accuracy of CT colonography screening and reduce reporting time. A third limitation is that colonoscopy was used as the reference standard; colonoscopy itself may miss some lesions and longer-term follow-up is needed to determine whether clinically significant lesions were missed.

In summary, in a group of persons at increased risk of CRC, CT colonography compared with colonoscopy resulted in a negative predictive value of 96.3% and a positive predictive value of 61.9% overall. When limited to FOBT-positive persons, the negative predictive value was 84.9%.

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