Randomized Trial of Different Screening Strategies for Colorectal Cancer: Patient Response and Detection Rates

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Background: **Although there is general consensus concerning the efficacy of colorectal cancer screening, there is a lack of agreement about which routine screening strategy should be adopted. We compared the participation and detection rates achievable through different strategies of colorectal cancer screening.** ***Methods:*** **From November 1999 through June 2001 we conducted a multicenter, randomized trial in Italy among a sample of 55–64 year olds in the general population who had an average risk of colorectal cancer. People with previous colorectal cancer, adenomas, inflammatory bowel disease, a recent (≤2 years) colorectal endoscopy or fecal occult blood test (FOBT), or two first-degree relatives with colorectal cancer were excluded. Eligible subjects were randomly assigned, within the roster of their general practitioner, to 1) biennial FOBT (delivered by mail), 2) biennial FOBT (delivered by general practitioner or a screening facility), 3) patient's choice of FOBT or "once-only" sigmoidoscopy, 4) "once-only" sigmoidoscopy, or 5) sigmoidoscopy followed by biennial FOBT. An immunologic FOBT was used. Participation and detection rates of the strategies tested were compared using multivariable logistic regression models that adjusted for age, sex, and screening center. All statistical tests were two-sided.** ***Results:*** **Of 28 319 people sampled, 1637 were excluded and 26 682 were randomly assigned to a screening arm. After excluding undelivered letters (*n* = 427), the participation rates for groups 1, 2, 3, 4, and 5 were 30.1% (682/2266), 28.1% (1654/5893), 27.1% (970/3579), 28.1% (1026/3650), and 28.1% (3049/10 867), respectively. Of the 2858 subjects screened by FOBT, 122 (4.3%) had a positive test result, 10 (3.5 per 1000) had colorectal cancer, and 39 (1.4%) had an advanced adenoma. Among the 4466 subjects screened by sigmoidoscopy, 341 (7.6%) were referred for colonoscopy, 18 (4 per 1000) had colorectal cancer, and 229 (5.1%) harbored an advanced adenoma.** ***Conclusions:*** **The participation rates were similar for sigmoidoscopy and FOBT. The detection rate for advanced neoplasia was three times higher following screening by sigmoidoscopy than by FOBT. [J Natl Cancer Inst 2005;97:347–57]**

There is a general consensus *(1–4)* that screening for colorectal cancer reduces mortality from and incidence of the disease. However, there is a lack of agreement about the preferred screening method. Screening strategies using a fecal occult blood test (FOBT) and sigmoidoscopy are currently being evaluated for implementation in population-based screening programs in several European countries (i.e., the United Kingdom, Norway, and Finland) and in Australia *(5–9)*. In Italy, the National Board for Oncology has issued guidelines recommending the implementation of pilot projects involving sigmoidoscopy and an FOBT for colorectal cancer screening *(10)*. Although colonoscopy is the most complete endoscopic procedure available for colorectal cancer screening *(11,12)*, direct evidence about its effectiveness, its complications, and its acceptability among individuals at average risk of the disease is still not sufficient to justify its use for routine screening *(13)*. Comparative data about neoplasia detection rates, participation rates, economic costs, and the side effects of the different screening strategies are needed to estimate the effectiveness and the balance between benefits and harms of screening interventions.

Only one large-scale trial has compared the performance of sigmoidoscopy and an FOBT in the same population of individuals at average risk of colorectal cancer *(14–16)*. However, in that trial, sigmoidoscopy was offered together with an FOBT. Such a strategy may have negatively affected the participation rate because of the longer time required for the study participants to complete all the necessary procedures (i.e., dietary restrictions, collection of three stool samples, and bowel preparation for sigmoidoscopy). Another problem with this trial was that all participating centers used a guaiac test to detect fecal occult blood, which has been shown to be less sensitive than immunochemical tests *(17,18)*.

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See "Notes" following "References."

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We conducted a randomized study comparing different screening strategies using an FOBT and sigmoidoscopy among 55–64 year olds. The objectives of the study were to assess the participation rate achievable through different strategies, to evaluate the acceptability and the safety of the proposed tests to the target population, to compare the detection rates of different strategies (particularly for early-stage colorectal cancer and advanced adenomas), and to estimate their costs. Cost estimates will be reported separately.

Subjects and Methods

Study Population and Design

We designed a population-based multicenter, randomized, controlled trial involving five Italian study centers located in Biella, Milan, Rimini, Turin, and Florence. A controlled trial of once-only sigmoidoscopy screening for colorectal cancer, the SCORE trial *(19)*, had been carried out in Biella, Milan, Rimini, and Turin from 1995 through 1999. Therefore, for these study centers, the procedure we designed to draw the population sample to be targeted for enrollment in our trial took into account the need to avoid recruitment of people who were already enrolled in the SCORE trial. Subjects were identified either through general practitioners' rosters or population registers. In Turin and Milan, the target population included all patients aged 55–64 years who were listed in the rosters of a random sample of general practitioners who had not been involved in the SCORE trial. In the other centers, the target population was recruited from those districts not yet involved in the SCORE trial (Biella and Rimini) or in the ongoing regional colorectal cancer screening program (Florence). All residents aged 55–64 years in those districts were targeted for recruitment: we identified and contacted their general practitioners, who were invited to collaborate in the study (Fig. 1).

At all locations, general practitioners were asked to exclude patients who were unable to give informed consent, who had been diagnosed with a terminal illness or inflammatory bowel disease, who had a history of polyps or colorectal cancer or two first-degree relatives with colorectal cancer, or who had undergone a colorectal endoscopy or an FOBT within the previous 2 years. We further excluded subjects already included in the SCORE trial who had changed their general practitioner to one that was included in this study or who had moved to a district included in current study area. General practitioners were also asked to sign the letters we provided that invited their patients to participate in this study as well as the mailed reminders and to provide the FOBT kit or the enema to the patient.

From November 1999 through June 2001, we randomly assigned all eligible patients aged 55–64 years, within the roster of their general practitioner, to one of five screening arms: 1) biennial FOBT sent by mail; 2) biennial FOBT delivered by general practitioner or screening facility (primary care or outpatient clinics); 3) patient's choice of FOBT or "once-only" sigmoidoscopy; 4) "once-only" sigmoidoscopy; or 5) sigmoidoscopy followed by biennial FOBT beginning 2 years after a sigmoidoscopy with negative findings. The randomization was performed in each center by the local coordinating unit, which used a computer-generated allocation algorithm, with an allocation ratio of two subjects (arm 1): five subjects (arm 2): three subjects (arm 3): three subjects (arm 4): nine subjects (arm 5). The allocation ratios were based on two criteria: the expected detection rates of advanced adenomas

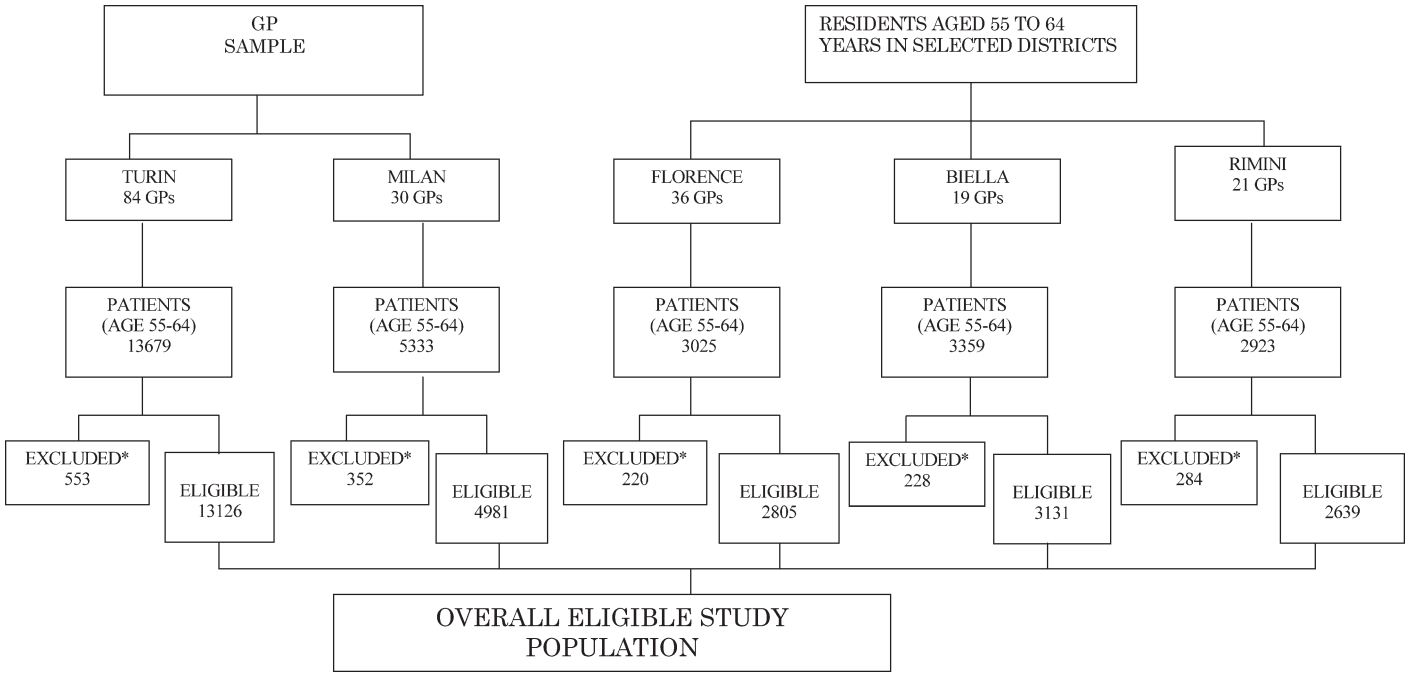

Fig. 1. Source population sampling by study center. Of the 190 general practitioners (GPs) contacted, 46 (24.2%) declined the offer to collaborate in this study and 144 (75.8%) agreed to sign the invitation letters; 82 of the GPs who agreed to sign the invitation letters also agreed to provide the FOBT kit to their patients who accepted the invitation to be screened. *A total of 1637 patients were excluded from this study because of a previous diagnosis of colorectal cancer, polyps, or inflammatory bowel disease (n = 297 [18.1%]), because they had been screened for colorectal cancer by a fecal occult blood test (n = 235 [14.4%]) or by endoscopy (n = 223 [13.6%]) within the previous 2 years, because they suffered from severe disease (n = 305 [18.6%]) or had severe psychiatric symptoms (n = 236 [14.4%]), or because they had moved from the study area before randomization (n = 341 [20.8%]).

and cancers among people undergoing an FOBT after negative results of a flexible sigmoidoscopy (arm 5) or among people allocated to flexible sigmoidoscopy or FOBT arms; the magnitude of differences in screening participation among different arms (see below under "Statistical Methods"). We generated a randomly ordered block of 22 interventions on this predefined allocation ratio. A random number was assigned to each eligible subject: subjects were then ordered within their general practitioner's list according to the random number assigned. The first subject in each general practitioner's list was randomly matched to one of the 22 interventions of the randomly ordered block. Starting from this matched intervention, blocks of 22 subjects allocated to the five study arms were automatically created for every general practitioner. Although subjects were randomly assigned on an individual basis, the algorithm assigned spouses to the same arm so that partners who were included in the trial were allocated to the same intervention.

Screening Procedure

Eligible subjects were mailed a personal invitation letter that was signed by their general practitioner (or by the local study coordinator, if the general practitioner refused to participate in the study). The mailing included a leaflet that briefly described the screening procedure and its possible side effects (text of leaflets available at http://jncicancerspectrum.oupjournals.org/jnci/content/vol97/issue5). All subjects who enrolled in the study provided written consent to the procedures indicated in the study protocol, which were performed without cost to the subject. This study was approved by the local ethics review committees.

Subjects allocated to the sigmoidoscopy screening arms were offered an appointment for a sigmoidoscopy at a specified time and were asked to call the screening center to confirm, modify, or cancel their appointment. Those who agreed to schedule a test date were advised to visit their general practitioner or the screening center to obtain the required enema kit. Subjects allocated to the FOBT screening arms received a letter that included a paper slide for stool smearing and instructions for performing the test (i.e., smearing modalities) and for storing and returning the sample or that invited the patient to contact his or her general practitioner or the screening center to obtain an FOBT kit and instructions for performing the test. A reminder letter was mailed to all subjects who did not respond to invitations to undergo screening by FOBT or sigmoidoscopy. Two additional invitations (consisting of personal letter signed by the general practitioner with a prespecified appointment) were sent 12 and 24 months after the first invitation to subjects who were allocated to the sigmoidoscopy arms and had not responded to the previous letters.

Assessment of Test Performance

FOBT. To detect fecal occult blood, we used an immunologic test that is based on reverse passive hemoagglutination (Immudia-HemSp, Fujirebio Inc., Tokyo, Japan) and can be performed on a single stool sample and does not require the subject to adhere to any dietary restriction. All FOBT cards collected in each study area were shipped weekly to one central laboratory (Laboratorio di Citopatologia, Centro per lo Studio e la Prevenzione Oncologica, Florence, Italy). The tests were developed with the use of a FASTEC 401, multi-channel type dispensing and dilution system (Fujirebio Inc.) according to the manufacturer's instructions. Results were interpreted with a FASTEC 901S, automated pattern reader (Fujirebio Inc.); results were considered positive if the specimen gave an agglutination reaction at a 1:8 dilution (which corresponds to an hemoglobin concentration of at least 0.2–0.3 mg blood/g feces). Subjects who had a positive test were called by the study staff, informed of the positive result of the test, and offered an appointment date for a colonoscopy. Subjects whose test results were negative were sent a letter informing them that the results were negative.

Sigmoidoscopy. Bowel preparation was limited to a single enema (consisting of 133 mL of 22% sodium phosphate) that the subject self-administered at home 2 hours before sigmoidoscopy. Dietary restriction was not required. Screening was performed in hospital endoscopy units by gastroenterologists. Before the sigmoidoscopy examination, all participants completed a questionnaire that asked about gastrointestinal symptoms they had experienced during the month preceding sigmoidoscopy, their family history of colorectal cancer, whether they had previously undergone colorectal endoscopy, and whether they were taking aspirin or anticoagulants. The sigmoidoscopy was performed with the use of a 140-cm colonoscope. The aim of the examination was to advance the colonoscope beyond the sigmoid-descending colon junction in subjects who had adequate bowel preparation. Although no medication (i.e., spasmolytic or sedative drugs) was offered to the subject, it could be administered if the endoscopist thought it was necessary. The endoscopist used a standard form to record information about the adequacy of bowel preparation, the reach of the colonoscope, the characteristics of any detected lesions, visualization of other findings, and the occurrence of complications. If the examination could not be performed because of inadequate bowel preparation, the subject was invited to repeat the test at a later date. After the examination, the endoscopist gave the subject a letter that explained the results and the limitations of the test. The letter specified an appointment date for a colonoscopy if large polyps had been detected or for receiving the histology results if small polyps had been excised during sigmoidoscopy. Subjects were advised to contact their general practitioner or the endoscopy unit if they experienced rectal bleeding or abdominal pain during the subsequent few days. A research assistant, who was not a member of the endoscopy staff, administered a short itemized questionnaire to all screenees after they had completed sigmoidoscopy; the questionnaire asked about the degree of pain and embarrassment subjects had experienced during the test.

Further Assessments and Management of Polyps

All polyps smaller than 10 mm detected during the sigmoidoscopy were immediately removed and sent for histologic assessment. Subjects with polyps that were 10 mm or larger, as well as those who had "high-risk" polyps smaller than 10 mm (i.e., patients whose polyps had any of the following features at histologic examination: more than two adenomas, a villous component of more than 20%, or high-grade dysplasia) were referred for colonoscopy. Subjects who had inadequate bowel preparation were also referred for colonoscopy if at least one polyp was identified during sigmoidoscopy. Colonoscopy was also recommended for all subjects who had a positive FOBT. Subjects who were suspected of having colorectal cancer or who had polyps that were too large to be removed endoscopically were referred

for surgery. A double-contrast barium enema was indicated when the colonoscopy could not be completed because of the patient's discomfort. If completion of the colonoscopy could not be achieved because of unsatisfactory bowel preparation, the patient was invited to repeat the examination.

Postpolypectomy Follow-up

Subjects who had negative sigmoidoscopy findings or were found to have hyperplastic polyps or "low-risk" adenomas (fewer than three tubular adenomas with low-grade dysplasia and smaller than 10 mm) were discharged from the endoscopy unit and were offered no further follow-up. A follow-up colonoscopy was scheduled at 3 years for all patients with "high-risk" adenomas (i.e., patients with any of the following: size 10 mm or larger, high-grade dysplasia, a villous component greater than 20%, or three or more adenomas of any type). Patients who had a positive FOBT and a negative colonoscopy (examination completed to the cecum without any finding) were scheduled to be invited to have an FOBT after 6 years.

Histologic Classification of Polyps and Colorectal Cancers

Histologic classification of polyps and cancers was based on World Health Organization criteria *(20)*. Advanced adenoma was defined as an adenoma with any of the following features: size 10 mm or larger, high-grade dysplasia, or a villous component of more than 20%. Cancer was defined as the invasion of malignant cells beyond the muscularis mucosae. Patients with intramucosal carcinoma or carcinoma in situ were classified as having high-grade dysplasia. To avoid inappropriate bowel surgery, the slides of screen-detected cancerous adenomas were reviewed by two pathologists. They were asked to assess features associated with the risk of nodal metastases *(21)* that could determine treatment options (open abdominal surgery versus endoscopic excision). All colorectal cancer samples and an equal-sized sample of adenomas with high-grade dysplasia were reviewed by one pathologist (M. Risio) in a blinded fashion; all of the original diagnoses were confirmed at this review.

Distal polyps were defined as those detected at screening sigmoidoscopy, including those lesions that were located beyond the sigmoid-descending colon junction as indicated in the endoscopist's report. Patients were classified on the basis of their most advanced lesion to determine the prevalence of pathologic features. Polyp size was classified according to the diameter of the largest polyp; for each polyp, we used the largest measure indicated by either the endoscopist or the pathologist. A colonoscopy was considered complete if the cecum could be visualized or, in the case of failure, when a subsequent colonoscopy performed within 6 months after the index one was able to reach the cecum. The combined results of the two exams were included in the analysis.

Statistical Methods

We planned to enroll 22 000 subjects: 3000 subjects each in Biella, Florence, and Rimini, 5000 subjects in Milan, and 8000 subjects in Turin. Given the randomization ratios, we expected that 273 subjects would be enrolled in the smallest arm (FOBT by mail) in centers in which we planned to enroll 3000 subjects. Assuming a participation rate of 30% in the comparison group and a 5% (two-tailed) level of statistical significance, these planned group sizes would give 80% power to detect an absolute difference in attendance of 10% within groups in each center and between centers for each group; a 5% absolute difference in participation (given the same assumptions) can be declared statistically significant when the results from all centers are combined. If we assume the same participation rate, the study size allowed us to consider a threefold increase in the detection rate at the initial screening for colorectal cancers and advanced adenomas in the sigmoidoscopy groups (once-only or sigmoidoscopy followed by FOBT) compared with the FOBT groups (delivered by mail or general practitioners or screening facilities) as statistically significant. This change to threefold increase is consistent with the detection rates for colorectal cancers and advanced adenomas observed in studies using an immunologic FOBT *(17,18)*, in studies comparing guaiac FOBT and sigmoidoscopy *(15,16)*, and in the sigmoidoscopy trials *(19,22)*.

Chi-square tests were used to test for statistical significance in comparisons of proportions. Odds ratios (ORs) and 95% confidence intervals (CIs) were used as a measure of association between the outcome of interest and the variables under evaluation in both unadjusted and multivariable analyses. For multivariable analyses, a logistic regression model was fitted to the data by using the SAS statistical package (version 8.2; SAS Institute, Cary NC). In this analysis, participation in screening and the presence of advanced adenomas or colorectal cancer were modeled as a function of screening modality, sex, age at screening, and, to allow for variability in participation and in adenoma or colorectal cancer detection rates, as a function of trial center. Separate models were fitted for FOBT-based screening (FOBT delivered by mail or by general practitioner/screening facilities) and for screening by sigmoidoscopy (either once-only or sigmoidoscopy followed by biennial FOBT). Only these latter groups (i.e., those in which patients were randomly assigned to receive a specific screening test) were considered in the analysis that compared the detection rate for neoplasms of the different screening strategies. All statistical tests were two-sided and were considered statistically significant at $P<.05$.

Results

Recruitment and Randomization

Among the 28 319 subjects aged 55–64 years who were listed in the rosters of the 190 general practitioners included in the study, 1637 subjects (5.8%; range = 4.0%–9.7% across the five trial centers) were excluded, and 26 682 subjects (range = 2 639–13 126 subjects) at the five centers were randomly assigned to one of the five study arms (Fig. 1). The proportions of randomized subjects by sex and age in each group (Table 1) corresponded to the age and sex distributions in the source populations for the five centers *(23)*.

Participation Rate

The participation rates for the different groups (Table 2) were calculated for the 26 255 subjects who received the invitation letter, after excluding 427 people who could not be traced (1.6% undelivered letters; range = 1.2%–2.6% across intervention groups). The overall participation rate among subjects who were sent an invitation to undergo an FOBT (either FOBT delivered by mail or by their general practitioner or a screening facility) was 28.6% (2336/8159; range = 21.8%–39.5% across the five trial

Table 1. Size of randomized groups by sex and age*

Screening arm	Men [*n* (%)]		Women [*n* (%)]		Total (*n*)
	55–59 years old	60–64 years old	55–59 years old	60–64 years old	
FOBT by mail	524 (22.5)	550 (23.6)	628 (27.0)	624 (26.8)	2326
FOBT by GP or screening facility	1476 (24.7)	1408 (23.5)	1569 (26.2)	1532 (25.6)	5985
Patient's choice	872 (24.0)	842 (23.2)	966 (26.6)	951 (26.2)	3631
Once-only sigmoidoscopy	917 (24.8)	825 (22.3)	963 (26.1)	990 (26.8)	3695
Sigmoidoscopy + biennial FOBT	2611 (23.6)	2484 (22.5)	2893 (26.2)	3057 (27.7)	11 045
Total	6400 (24.0)	6109 (22.9)	7019 (26.3)	7154 (26.8)	26 682

*FOBT = fecal occult blood test; GP = general practitioner.

Table 2. Participation rate by sex, age, and screening arm*

Screening arm	Women				Men				Total	
	55–59 years old		60–64 years old		55–59 years old		60–64 years old			
	No. invited	No. attended (%)	No. invited	No. attended (%)	No. invited	No. attended (%)	No. invited	No. attended (%)	No. invited	No. attended (%)
FOBT by mail	528	182 (34.5)	702	228 (32.5)	447	107 (23.9)	589	165 (28.0)	2266	682 (30.1)
FOBT by GP or screening facility	1317	397 (30.1)	1750	497 (28.4)	1238	320 (25.8)	1588	440 (27.7)	5893	1654 (28.1)
Once-only sigmoidoscopy	873	231 (26.5)	1061	280 (26.4)	806	258 (32.0)	910	257 (28.2)	3650	1026 (28.1)
Sigmoidoscopy + biennial FOBT	2517	692 (27.5)	3343	835 (25.0)	2237	707 (31.6)	2770	815 (29.4)	10 867	3049 (28.1)
Patient's choice	806		1084		743		946		3579	
FOBT		120 (14.9)		171 (15.8)		98 (13.2)		133 (14.1)		522 (14.6)
Sigmoidoscopy		99 (12.3)		130 (12.0)		100 (13.5)		119 (12.6)		448 (12.5)
Total		219 (27.2)		301 (27.8)		198 (26.6)		252 (26.6)		970 (27.1)
Total	6041	1721 (28.5)	7940	2141 (27.0)	5471	1590 (29.1)	6803	1929 (28.4)	26 255	7381 (28.1)

*Undelivered invitations are excluded from the denominator (i.e., No. invited). FOBT = fecal occult blood test; GP = general practitioner.

centers); the participation rate among subjects who were sent an invitation to have sigmoidoscopy (either once-only sigmoidoscopy or sigmoidoscopy followed by biennial FOBT) was 28.1% (4 075/14 517; range = 22.3%–33.6%). The difference between these participation rates was not statistically significant. In the largest centers (Milan and Turin), the participation rate for FOBT screening was only slightly lower than that for sigmoidoscopy; in Rimini (OR = 1.29; 95% CI = 1.08 to 1.54) and Florence (OR = 1.33; 95% CI = 1.12 to 1.59) participation was statistically significantly higher in the FOBT groups than in the sigmoidoscopy groups (data not shown).

Mailed reminders were associated with an absolute increases of 9.2% and 11.1% in the participation rates among subjects invited to undergo an FOBT delivered by mail and an FOBT delivered by general practitioner or a screening facility, respectively. Mailed reminders were associated with absolute increases of 3.3% and 3.2% in the participation rate among subjects invited to undergo once-only sigmoidoscopy and sigmoidoscopy followed by biennial FOBT, respectively. The two additional invitations with prefixed appointments at 12 and 24 months after the initial invitation were associated with an absolute increases of 5.9% and 5.6% in the participation rate among subjects in the once-only sigmoidoscopy group and in the sigmoidoscopy followed by biennial FOBT group, respectively. Mail delivery of the FOBT kit was associated with a 2% absolute increase in participation rate. The participation rate did not increase when subjects were offered a choice between FOBT and sigmoidoscopy screening compared with an invitation to participate in one of these strategies.

We estimated the participation rates in a multivariable model after mutually adjusting for the effects of the covariates (age, sex, center, and screening arm) on participation. The participation rate in the sigmoidoscopy groups was higher among men than among women (OR = 1.22, 95% CI =1.14 to 1.32) and lower among subjects aged 60–64 years than among subjects aged 55–59 years (OR = 0.89; 95% CI = 0.82 to 0.95) (Table 3). Among the subjects invited for FOBT screening, fewer men than women actually took the test (OR = 0.82, 95% CI = 0.74 to 0.90). Overall, more subjects who had been sent an FOBT kit actually took the test than subjects who were allocated to the sigmoidoscopy followed by biennial FOBT group (OR = 1.11, 95% CI = 1.00 to 1.22, P = .0498); the participation rates in all other screening arms were similar to that for the sigmoidoscopy followed by biennial FOBT arm. Overall, subjects aged 60–64 years had lower screening participation rates than subjects aged 55–59 years (OR = 0.94, 95% CI = 0.89 to 0.99), independent of screening modality. When we restricted the analysis to subjects in the older age group, the participation rate to the invitation for FOBT was higher than the participation rate to sigmoidoscopy screening (OR = 1.09, 95% CI = 1.01 to 1.18) (data not shown).

Screening Results and Management of Study Participants

Among the 2336 subjects who were allocated to the FOBT arms (i.e., FOBT delivered by mail or by general practitioner or screening facility) and actually took the test, 108 (4.6%) had a positive test result and 95 of them underwent colonoscopy (Table 4). Eight colorectal cancers (corresponding to a cancer detection rate of 3.4 cancers per 1000 persons screened) and 35 advanced adenomas (1.5% of subjects screened) were detected by colonoscopy. In 11 cases (four colorectal cancers and seven advanced adenomas), the most advanced lesion was located proximal to the sigmoid-descending colon junction. The positive predictive value (PPV) of an FOBT for advanced neoplasia (colorectal

Table 3. Odds ratio for participation rate by age, sex, and screening arm in the FOBT and sigmoidoscopy arms and in whole study population*

	n	OR† (95% CI)
FOBT arms		
FOBT by GP or screening facility	5893	1.00 (referent)
FOBT by mail	2266	1.11 (0.99 to 1.23)
55–59 years old	3530	1.00 (referent)
60–64 years old	4629	1.01 (0.92 to 1.11)
Women	4297	1.00 (referent)
Men	3862	0.82 (0.74 to 0.90)
Sigmoidoscopy arms		
Sigmoidoscopy + biennial FOBT	10867	1.00 (referent)
Once-only sigmoidoscopy	3650	1.00 (0.92 to 1.09)
55–59 years old	6433	1.00 (referent)
60–64 years old	8084	0.89 (0.82 to 0.95)
Women	7794	1.00 (referent)
Men	6723	1.22 (1.14 to 1.32)
Whole study population		
Sigmoidoscopy + FOBT	10867	1.00 (referent)
Once-only sigmoidoscopy	3650	1.00 (0.92 to 1.09)
Patient's choice	3579	0.95 (0.88 to 1.04)
FOBT by GP or screening facility	5893	1.00 (0.93 to 1.07)
FOBT by mail	2266	1.11 (1.00 to 1.22)
55–59 years old	11512	1.00 (referent)
60–64 years old	14743	0.94 (0.89 to 0.99)
Women	13981	1.00 (referent)
Men	12274	1.05 (0.99 to 1.10)

*FOBT = fecal occult blood test; OR = odds ratio; CI = confidence interval; GP = general practitioner.

†Multivariable ORs adjusted for screening center and for all the other variables in the table.

cancer or advanced adenoma) was 45.3% (43/95; range = 33.3%–62.5% across study centers). When we adjusted for sex and screening center, the prevalence of advanced neoplasia was statistically significantly higher among subjects aged 60–64 years than among those aged 55–59 years (OR = 3.41, 95% CI = 1.51 to 7.70), with a corresponding increase in the PPV of an FOBT from 25.9% among the younger age group to 52.9% among the older subjects (data not shown). The prevalence of advanced adenomas was fivefold higher among subjects aged 60–64 years than among subjects aged 55–59 years (OR = 5.10, 95% CI = 1.79 to 14.50) (Table 5). Among the 522 subjects in the patient's choice screening arm who chose to undergo FOBT screening, 14 (2.7%) had a positive test result and 12 of those subjects underwent colonoscopy; four subjects (0.8%) were found to have an advanced adenoma and two subjects (0.4%) had colorectal cancer (Table 4).

Overall, therefore, 122 of the 2858 subjects who underwent an FOBT (4.3%; range = 3.3%–4.6% across study centers) had a positive test result. Of these 122 subjects, 12 refused to undergo colonoscopy, three underwent a double-contrast barium enema (a radiologic examination that looks for polyps or cancer in the colon or rectum; for all three subjects, the examination result was negative), and 107 (87.7%) underwent colonoscopy. Colonoscopy could be completed to the cecum in 76.6% (82/107) of these subjects. Of the 25 patients with an incomplete colonoscopy, seven refused further assessments, two (one with advanced

Table 4. Most advanced lesions (distal or proximal) identified through screening by sex, age, and screening arm*

	Women		Men		55–59 years old		60–64 years old		Total	
Screening arm	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
FOBT (by mail or by GP or screening facility)										
Patients screened	1304	100	1032	100	917	100	1419	100	2336	100
FOBT positive	53	4.1	55	5.3	33	3.6	75	5.3	108	4.6
Colonoscopy performed†	46	86.8	49	89.1	27	81.8	68	90.7	95	88.0
Low-risk adenomas	1	0.1	2	0.2	1	0.1	1	0.1	2	0.1
Advanced adenomas	17	1.3	18	1.7	4	0.4	31	2.2	35	1.5
Colorectal cancer	2	0.2	6	0.6	3	0.3	5	0.4	8	0.3
FOBT (patient's choice)										
Patients screened	291	100	231	100	195	100	327	100	522	100
FOBT positive	8	2.7	6	2.6	5	2.6	9	2.8	14	2.7
Colonoscopy performed†	8	100.0	4	66.7	5	100.0	7	77.8	12	85.7
Low-risk adenomas	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Advanced adenomas	2	0.7	2	0.9	2	1.0	2	0.6	4	0.8
Colorectal cancer	2	0.7	0	0.0	2	1.0	0	0.0	2	0.4
Sigmoidoscopy (once-only sigmoidoscopy or sigmoidoscopy + FOBT)										
Patients screened	2012	100	2013‡	100	1661	100	2364‡	100	4025	100
No findings	1753	87.1	1524	75.7	1360	81.9	1917	81.1	3277	81.4
Non-neoplastic polyps§	74	3.7	167	8.3	102	6.1	140	5.9	242	6.0
Low-risk adenomas	98	4.9	181	9.0	112	6.7	166	7.0	279	6.9
Advanced adenomas	82	4.1	131	6.5	83	5.0	130	5.5	213	5.3
Colorectal cancer	5	0.2	9	0.4	4	0.2	10	0.4	14	0.3
Sigmoidoscopy (patient's choice)										
Patients screened	224	100	217	100	183	100	258	100	441	100
No findings	187	83.5	172	79.3	157	85.8	202	78.3	359	81.4
Non-neoplastic polyps§	15	6.7	20	9.2	12	6.6	23	8.9	35	7.9
Low-risk adenomas	12	5.4	15	6.9	9	4.9	18	7.0	27	6.1
Advanced adenomas	8	3.6	8	3.7	4	2.2	12	4.7	16	3.6
Colorectal cancer	2	0.9	2	0.9	1	0.5	3	1.2	4	0.9

*FOBT = fecal occult blood test; GP = general practitioner.

†All subjects with a positive FOBT were referred for colonoscopy.

‡One patient refused to undergo colonoscopy, and therefore his polyp was not excised.

§Hyperplastic polyps, normal or inflammatory mucosa, inadequate samples, and missed polyps are included in this category.

Table 5. Odds ratio for advanced adenomas in FOBT and sigmoidoscopy arms by age and sex and among all patients examined, excluding those in the patient's choice arm, by age, sex, and screening test*

	n	OR† (95% CI)
FOBT arms (by mail or by GP or screening facility)		
55–59 years old	917	1.00 (referent)
60–64 years old	1419	5.10 (1.79 to 14.50)
Women	1304	1.00 (referent)
Men	1032	1.34 (0.68 to 2.62)
Sigmoidoscopy arms (once-only or sigmoidoscopy + FOBT)		
55–59 years old	1661	1.00 (referent)
60–64 years old	2364	1.13 (0.85 to 1.50)
Women	2012	1.00 (referent)
Men	2013	1.66 (1.25 to 2.20)
All patients examined excluding those in patient's choice arm		
FOBT arms	2336	1.00 (referent)
Sigmoidoscopy arms	4025	3.58 (2.49 to 5.14)
55–59 years old	2578	1.00 (referent)
60–64 years old	3783	1.32 (1.01 to 1.72)
Women	3316	1.00 (referent)
Men	3045	1.61 (1.24 to 2.09)

*FOBT = fecal occult blood test; GP = general practitioner; OR = odds ratio; CI = confidence interval.

†Multivariable ORs adjusted for screening center and for all the other variables in the table.

adenoma and one with non-neoplastic polyps) were rescheduled for a subsequent colonoscopy within 12 months, and one patient with colorectal cancer was referred for surgery. The remaining 15 patients (seven with advanced adenomas, one with one tubular adenoma smaller than 10 mm, and seven with negative examination results) underwent double-contrast barium enema, which did not detect any additional lesion. Two (20%) of 10 colorectal cancers were treated endoscopically only.

Among the 4025 subjects screened in the sigmoidoscopy arms (i.e., once-only sigmoidoscopy or sigmoidoscopy followed by biennial FOBT), the prevalence of polyps was 18.6% (Table 4). Adenomas were detected in 492 subjects (12.2%; range = 11.0%–12.5% across study centers). A colorectal cancer was detected in 14 of 4025 subjects examined (corresponding to a detection rate of 3.5 cancers per 1000 persons screened): all colorectal cancers were detected by sigmoidoscopy (including two located in the descending colon). Among the 310 subjects who underwent colonoscopy, the prevalence of adenomas in the proximal colon was 16.2%; 17 subjects (5.5%) were detected with advanced proximal adenomas. For five patients, the most advanced lesion was located in the proximal colon. After adjusting for age and screening center, the prevalence of advanced adenomas was statistically significantly higher among men than among women (OR = 1.66, 95% CI = 1.25 to 2.20) (Table 5).

Among the 441 subjects in the patient's choice screening arm who chose to undergo sigmoidoscopy screening, 16 (3.6%) were found to have an advanced adenoma and four (0.9%) had colorectal cancer (Table 4).

Overall, therefore, in 3606 (79.7%) of the 4523 subjects who underwent sigmoidoscopy, the test could be completed to the distal descending colon during the first attempt (Fig. 2). For 369 of the 917 subjects who had incomplete sigmoidoscopy, inadequate bowel cleaning prevented visualization of any segment of the bowel mucosa. These patients were offered a new test date; 312 accepted, and the examination was completed in 273. Therefore, 4466 of the 4523 subjects who underwent sigmoidoscopy had a complete (n = 3879 [86.9%]) or partial (n = 587 [13.1%]) examination of the distal bowel (Fig. 2). Of the 587 subjects with an incomplete examination because of reasons other than inadequate bowel preparation (e.g., the patient complained of too much pain or the insertion of the scope was too difficult due to bowel adhesions), 103 were referred for colonoscopy, four were referred for surgery (three had colorectal cancer and one had a large adenoma); among the 480 subjects who were discharged, 35 had low-risk polyps (hyperplastic polyps or one or two tubular adenomas with low-grade dysplasia and size smaller than 10 mm) and 445 subjects harbored no lesion in the segments of the colon examined. Of the 4466 subjects who were screened by sigmoidoscopy, 341 (7.6%) were referred for colonoscopy, and 332 of them (97.4%) had the examination (Fig. 2). Colonoscopy could not be completed to the cecum in 43 of these 332 subjects (13.0%): 19 subjects had a repeat colonoscopy within 12 months, 17 underwent a double contrast barium enema, and seven refused further assessments. Overall, of the 4466 subjects screened by sigmoidoscopy, 248 (5.6%) had a subsequent surveillance colonoscopy, 4189 (93.8 %) were discharged, nine (0.2%) refused to complete the prescribed assessments, and 20 (0.4%) were referred for surgery (13 had colorectal cancer and seven had adenomas that were too large to be removed safely at endoscopy) (Fig. 2). Five (27.8%) of 18 colorectal cancers detected among the 4466 subjects who had sigmoidoscopy were treated endoscopically only.

Comparison of Neoplasia Detection Rates

Among subjects randomly assigned to the sigmoidoscopy (once-only or sigmoidoscopy followed by FOBT) or the FOBT (delivered by mail or by general practitioner or screening facilities) arms, the detection rate for advanced adenomas (adjusted by age, sex, and screening center) was statistically significantly higher for sigmoidoscopy than for FOBT (OR = 3.58, 95% CI = 2.49 to 5.14) (Table 5). The proportion of adenomas 10 mm or larger presenting with a villous component of greater than 20% or high-grade dysplasia was 63.5% for sigmoidoscopy-detected lesions and 61.3% for FOBT-detected lesions (data not shown).

The adjusted colon cancer detection rate was approximately the same for sigmoidoscopy as it was for FOBT (OR = 0.99, 95% CI = 0.41 to 2.36; data not shown); when we considered distal lesions only, the colorectal cancer detection rate for sigmoidoscopy was twice as high as that for FOBT, but the difference was not statistically significant (OR = 2.13, 95% CI = 0.70 to 6.43; data not shown). One of the eight colorectal cancers detected by FOBT screening and five of the 14 colorectal cancers detected by sigmoidoscopy were treated endoscopically only. Assuming that these cases were localized disease, a total of 12 (85.7%) of the 14 cancers in the sigmoidoscopy groups and three (37.5%) of the eight cancers in the FOBT groups were either presumptive or proven Dukes' stage A colorectal cancers.

Side Effects and Patients' Experiences of Screening

Among the 4466 subjects who underwent sigmoidoscopy, five (0.1%) experienced self-limited bleeding following polypectomy and 16 (0.4%) complained of mild vagal reactions (nausea, feeling faint, or dizzy). A 61-year-old woman had a severe vagal reaction

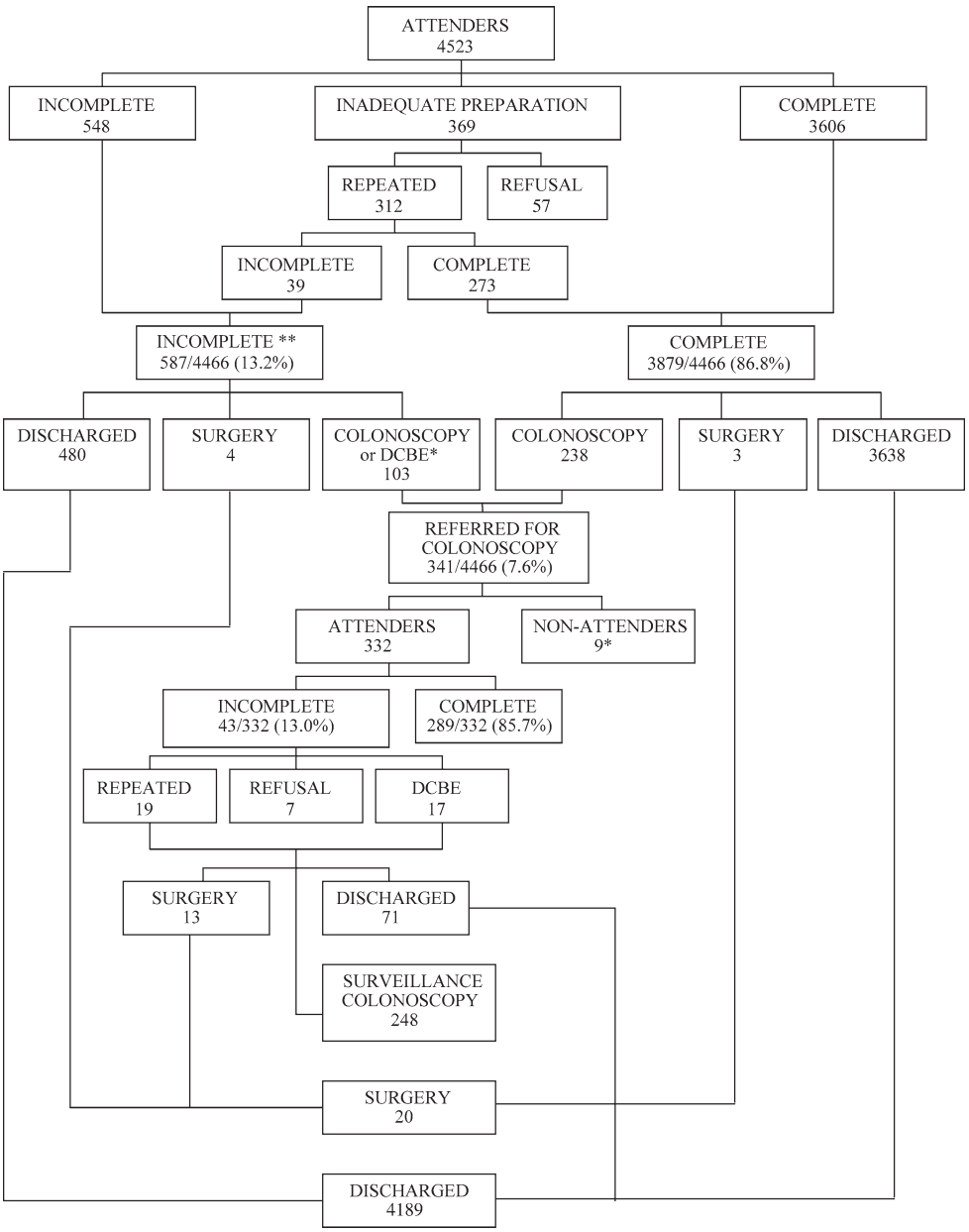

Fig. 2. Management of sigmoidoscopy subjects (all arms performing sigmoidoscopy): number of patients and proportion (%). *One patient was referred for double contrast barium enema (DCBE); no lesion detected in the proximal colon. **Specific reasons for stopping the test in 480 of the 587 patients with incomplete endoscopy were inadequate bowel preparation in 214 cases, patient's pain in 92 cases, and bowel adhesions in 139 cases (the reason for stopping the test was not specified in 35 cases); among the remaining patients with incomplete endoscopy, 103 were referred for colonoscopy and four were referred for surgery.

and an apparent cardiac arrest while undergoing a sigmoidoscopy examination; she was resuscitated and subsequently discharged from the hospital within 24 hours. Of the 332 patients who underwent colonoscopy, eight (2.4%) experienced self-limited bleeding following polypectomy and five (1.5%) complained of mild vagal reactions, but none of them was referred to a hospital. One patient experienced severe hemorrhage requiring hospitalization 3 days after colonoscopy.

Of the 4466 subjects examined with sigmoidoscopy, 4268 (95.6%) completed the short questionnaire administered immediately after sigmoidoscopy: 62.3% reported that they had experienced mild pain, 25.4% reported that the test was less painful than they had expected, and only 1.2% described the pain as "the most severe ever experienced." Women reported higher levels of pain than men (OR of reporting "the most severe pain I ever experienced" or "I hope it will not be necessary to repeat the test" versus "mild" or "less pain than expected" = 2.32, 95% CI = 1.90 to 2.83). In addition, endoscopists indicated that the examination had to be stopped because of bowel adhesions more frequently among women than among men (OR = 2.31, 95% CI = 1.40 to 3.84).

Discussion

This is the first large trial to compare the participation and detection rates of different screening tests and strategies for colorectal cancer in a population at average risk for the disease. Overall, approximately 28% of the people invited were screened. The participation rate for FOBT screening in Florence was similar to the participation rate for the screening program that was running at the time of trial recruitment in other areas of Tuscany in which subjects were invited to have an FOBT every 2 years *(24)*. Similarly, the 27% participation rate among subjects invited for sigmoidoscopy screening in Turin was the same as that achieved in the pilot phase of the SCORE trial among people aged 55–59 years who were at average risk of colorectal cancer *(25)*. Therefore, subjects in our trial who were screened are likely to

be representative of people from the general population of these same regions of Italy who might participate in any mass screening program for colorectal cancer starting now. Public awareness of colorectal cancer is not yet widespread in Italy, which may explain the low participation rate. A higher participation rate might be achieved in the context of an established screening program that would cover the whole population through mass-media campaigns, which were not implemented in the context of the trial. However, because we randomly assigned all eligible subjects individually within the roster of each general practitioner included in the trial, the observed rates probably reflect the actual relative differences between the strategies tested. Therefore, our findings suggest that, in a mass screening program for colorectal cancer in Italy, there would be no substantial difference in participation rates between subjects invited to undergo screening by FOBT and those invited to undergo screening by sigmoidoscopy.

The effect of a single FOBT in protecting against fatal colorectal cancer appears to abate after 2 years (guaiac test) *(26)* or 3 years (immunologic test) *(26,27)*, whereas the protective effect of a single sigmoidoscopy examination may extend for more than 10 years *(28,29)*. Therefore, for FOBT and sigmoidoscopy to produce comparable benefits with respect to colorectal cancer mortality, regular attendance over several screening rounds is required for an FOBT, whereas only one round of screening by sigmoidoscopy over the same period is necessary.

The participation rate achieved with three consecutive invitations for sigmoidoscopy over 2 years (i.e., the interval between two FOBTs), was approximately 0.5% lower than the attendance rate at the first FOBT screening round. Published data from FOBT trials *(30,31)* indicate that the response rate at a second invitation among people who attended the first screening varies between 85% and 90%, but it tends to decrease over subsequent rounds, to 50%–70% after four to five rounds. Our data therefore suggest that by the second FOBT screening round the coverage may be similar using either sigmoidoscopy or FOBT, when taking into account the duration of the protective effect of the tests and the proportion of regular attenders to an FOBT.

We found that the participation rate was the same regardless of whether subjects could choose or were assigned to a screening strategy. In the context of this trial, information about the characteristics of the screening tests was conveyed mainly through written material. The leaflet, mailed together with the invitation letter, presented data about benefits and risks of the proposed tests and described the test procedures. However, this approach may constitute a barrier to attendance because subjects may find it difficult to understand probabilistic estimates of benefits and risks and may have little confidence in relying on written information alone to make health-related decisions *(32–34)*.

Direct mailing of an FOBT kit has been shown to be associated with a statistically significant increase in the self-reported use of FOBT screening, compared with a community-wide screening promotion campaign *(35)*. We also found that the way in which an FOBT kit was delivered to subjects was associated with a small but statistically significant difference in attendance rate. The impact of mailing FOBT kits to subjects on participation was larger in those centers (Biella, Rimini, and Turin) where only one facility was available for FOBT kit distribution. However, sending an FOBT kit by mail costs more than mailing a letter, and an average of 70% of the kits sent by mail were not returned (i.e., the participation rate was 30% in the FOBT by mail group). Therefore, the costs of such a strategy should be balanced against the resources needed to open more facilities for FOBT kit distribution and/or to promote general practitioners' collaboration in the delivery of FOBT kits to their patients.

Women had a lower participation rate in sigmoidoscopy screening than men, especially within the younger age group. Among subjects who had sigmoidoscopy, a statistically significantly higher proportion of women than men reported having painful experience with the test. In addition, the proportion of examinations that could not be completed because of bowel adhesions was statistically significantly higher among women than among to men. Similar findings were previously reported *(36)*. These findings suggest that specific interventions that address barriers to attendance among women as well as aspects related to test performance in women should be implemented in any mass screening program that adopts sigmoidoscopy.

Although the immunologic FOBT adopted in this trial had a higher positivity rate than that reported for the FOBT trials that used an unhydrated guaiac test *(37,38)*, we did not observe a substantial decrease in the PPV for large adenomas and cancers, compared with the predictivity of the guaiac test in those trials. Thus, the higher proportion of colonoscopy referrals with an immunologic FOBT compared with a guaiac FOBT resulted in the detection of a larger number of neoplasms. Indeed the detection rate of the immunologic FOBT was about twice as high both for colorectal cancer and adenomas 10 mm or larger in our trial compared with figures reported from other studies using unhydrated Hemoccult-II. This result is consistent with the findings from other authors showing a higher sensitivity and a more prolonged protective effect of the immunologic FOBT *(17,18,25,26)*. Self-selection of patients at increased risk of colorectal cancer cannot be excluded, given the low rate of participation in our study, but it seems unlikely that it can explain the magnitude of the observed effect. We did not check for the presence of gastrointestinal symptoms, which are poor predictors of colorectal neoplasia *(39–41)*.

The detection rate of advanced neoplasia was statistically significantly higher for sigmoidoscopy than for FOBT. This difference was attributable mainly to an approximately threefold increase in the detection rate of advanced adenomas, consistent with previous findings of studies comparing the yield of sigmoidoscopy and FOBT. It has been suggested that advanced adenomas should be considered to be appropriate targets for screening given their greater risk of progression over a short interval *(13)*. Because the proportion of advanced adenomas presenting with features that have been shown to be associated with an increased risk of progression [i.e., a villous component greater than 20% and high-grade dysplasia *(20,42)*] is the same for FOBT- and sigmoidoscopy-detected neoplasms, the higher yield of lesions achieved with sigmoidoscopy than with FOBT screening supports the hypothesis that sigmoidoscopy screening might have a larger impact on colorectal cancer incidence than FOBT screening, as suggested by other studies *(28,29,43,44)*. These findings also suggest that the most important advantage of sigmoidoscopy is its ability to prevent colorectal cancer through detection and excision of precursors of the malignant lesions. Although the detection rate for distal colorectal cancer among patients undergoing sigmoidoscopy was twice as high as that among patients who had an FOBT, the overall colorectal cancer yield achieved using these strategies was the same. The stage distribution of colorectal cancers detected at sigmoidoscopy screening tended to be more favorable than the stage distribution of colorectal cancers detected by an

FOBT. However, it should be noted that the absolute number of colorectal cancers detected in our study was too low to allow us to make precise estimates of the relative performances of the tests. We plan to compare the detection rates of the tests for colorectal cancers after two subsequent screening rounds.

Our comparison of the detection rate of FOBT and sigmoidoscopy screening is limited by the fact that we considered only one round of FOBT screening. To obtain more accurate estimates of the detection rate of these two strategies and to compare the costs of detecting an advanced lesion associated with each strategy, the results of several FOBT screening rounds should be considered. An analysis that compared the results of two independent trials *(45)* showed that biennial screening with an unhydrated guaiac test (a traditional guaiac test for fecal occult blood) detected a similar number of advanced adenomas over eight screening rounds (16 years) as a single screening with sigmoidoscopy: the cumulative detection rate for colorectal cancer was similar after five FOBT screening rounds, and it was statistically significantly increased at 16 years in the FOBT trial, compared with the single sigmoidoscopy study. Follow-up results of the once-only sigmoidoscopy trials *(19,22),* which will be available in a few years, will allow a more precise estimate of the duration of the protective effect of sigmoidoscopy.

In conclusion, our results suggest that both FOBT and sigmoidoscopy are feasible and acceptable tests for population-based colorectal cancer screening programs. The implications of choosing a screening strategy are profound; therefore, pilot testing of possible screening options at the population level is important so that adequate information about the cost-effectiveness, feasibility, and detection rates for cancer and advanced adenomas of the proposed strategies can be obtained. In population screening, the participation rate is crucial to success. When two tests that have different durations of protective effect are compared, a comparison of population cumulative participation that is achievable over a certain period of time may be equally relevant. A trial with a sequential invitation to undergo sigmoidoscopy for nonresponders to an FOBT, and vice versa, would be necessary to estimate the proportion of people who would accept only a specific test (either FOBT or sigmoidoscopy) or who would participate independently of the test offered and to estimate neoplasia yield.

Our results also suggest that, during the 2-year period of our study, the proportion of people screened with sigmoidoscopy or with FOBT was similar. The evaluation of the impact of these strategies should therefore take into account their costs and the number of tests required to achieve the same yield of advanced neoplasia. Other crucial aspects to be considered in the implementation and assessment of colorectal cancer screening interventions are information about patients' preferences and effective communication between patients and their health care providers about the risks and benefits of colorectal cancer screening.

Appendix

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