Baseline Findings of the Italian Multicenter Randomized Controlled Trial of "Once-Only Sigmoidoscopy"—SCORE

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Background: **A single sigmoidoscopy examination at around age 60 years has been proposed as a cost-effective strategy to prevent colorectal cancer. A multicenter randomized controlled trial, the SCORE trial, is in progress in Italy to estimate the impact of this strategy on colorectal cancer incidence and mortality and the duration of the protective effect. We present the baseline screening outcomes.** ***Methods:*** **A questionnaire was mailed to a random sample of 236 568 people aged 55–64 years to assess their eligibility for and interest in screening. Those reporting a history of colorectal cancer, adenomas, inflammatory bowel disease, recent colorectal endoscopy, or two first-degree relatives with colorectal cancer were excluded. Eligible, interested respondents were assigned randomly to the control group (no further contact) or the intervention group (invitation to undergo sigmoidoscopy). Screenees with colorectal cancer, polyps larger than 5 mm, three or more adenomas, adenomas 5 mm or smaller with a villous component of more than 20%, or severe dysplasia were referred for colonoscopy.** ***Results:*** **Of the 56 532 respondents (23.9% of those invited), 34 292 were enrolled and 17 148 were assigned to the screening group. Of those, 9999 attended and 9911 were actually examined by sigmoidoscopy. Distal adenomas were detected in 1070 subjects (10.8%). Proximal adenomas were detected in 116 of 747 (15.5%) subjects without cancer at sigmoidoscopy who then underwent colonoscopy. A total of 54 subjects was found to have colorectal cancer, a rate of 5.4 per 1000 (54% of which were Dukes' A). The procedures were relatively safe, with two perforations (one in 9911 sigmoidoscopy exams and one in 775 colonoscopies) and one hemorrhage requiring hospitalization after polypectomy during colonoscopy. The pain associated with sigmoidoscopy was described as mild or less than expected by 83.3% of the screenees.** ***Conclusion:*** **Sigmoidoscopy screening is generally acceptable to recipients and safe. The high yield of advanced adenomas is consistent with the projected impact of sigmoidoscopy screening on colorectal cancer incidence. [J Natl Cancer Inst 2002;94: 1763–72]**

Colorectal cancer is the second leading cause of cancer death in Europe *(1).* In Italy, mortality rates from the disease have remained fairly constant over the past decade, with approximately 17 000 deaths per year *(2).* Based on projections from past trends, about 40 000 new cases were expected in 2000 in Italy *(3).* Several observational and intervention studies have shown consistent and marked reductions in both colorectal cancer incidence *(4–8)* and mortality *(9,10)* following colorectal endoscopy and polypectomy. These studies showed a protective effect of screening only for the colonic segments examined *(4–10)* that was maintained for up to 10 years *(9).* The Minnesota trial of fecal occult blood testing *(11)* was the first large trial to show a reduction of incidence of colorectal cancer following screening-related endoscopy.

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See "Notes" following "References."

The protective effect of endoscopic polipectomy supports the hypothesis that colorectal carcinomas arise from adenomas, with an estimated average transition time to malignancy of approximately 10–15 years *(12–14).* Based on these findings, it was estimated that a single sigmoidoscopy screen might be a cost-effective and feasible strategy for colorectal cancer screening among individuals at average risk for the disease *(15).* Two further observations provide support for the idea that a single sigmoidoscopy screen may be effective in preventing a considerable proportion of colorectal cancer: the prevalence of distal adenomas in asymptomatic individuals appears to reach a plateau at around the age of 60 years *(15),* and data from European Cancer Registries show that among patients aged 55–74 years about two thirds of colorectal carcinomas are located in the rectum or sigmoid colon *(16).*

A controlled trial of "once-only" sigmoidoscopy screening for colorectal cancer (the SCORE trial) was undertaken in Italy as a parallel study to a multicenter trial in the United Kingdom *(17,18).* The goal of these trials was to measure the extent of reduction in colorectal cancer incidence and mortality achieved by a single screening sigmoidoscopy examination and to determine both the optimum age interval (i.e., 55–59 or 60–64 years of age) for screening and the duration of the protective effect of a single test. The recruitment and screening phases of the SCORE trial have now been completed. Here we report on results concerning the neoplasia detection rate and safety and acceptability of this method of screening.

Subjects and Methods

Study Population

Approval for the study was granted by the local ethics review committees in each center. Subjects were identified either through physicians or directly. In Arezzo, Rimini, and Torino, the target population was selected from the patients of a random sample of general practitioners drawn from the National Health Service (NHS) list of those working in the study areas. In Milano, the patients were selected from the list of all general practitioners who were invited and volunteered to cooperate. In Genova and Biella, a random sample of individuals in the target age range was drawn directly from the NHS register. All individuals aged 55–64 years included in these samples (that is, resident in the study areas and listed in the NHS lists that provided their names) were mailed a questionnaire designed to assess their eligibility for and interest in screening, with an accompanying letter giving brief information about the sigmoidoscopy and explaining the rationale for the study. A prepaid envelope for returning the questionnaire was also provided. No reminder was sent to nonresponders. Responders were excluded if they reported a history of colorectal cancer, colorectal polyps, or inflammatory bowel disease had had a colorectal endoscopy within the previous 2 years; had two or more first-degree relatives with colorectal cancer; or had a medical condition that would preclude benefit from screening.

Random Assignment and Invitation for Screening

People who answered that they were probably or definitely not interested in screening were not contacted again. Eligible respondents who indicated that they would definitely or probably undergo screening sigmoidoscopy if it were offered to them were assigned randomly to the intervention or control group in a 1 : 1 ratio. Random assignment was performed in each center by the local coordinating unit with the use of a computer-generated allocation algorithm. In Biella, Genova, and Milano, subjects were assigned randomly on an individual basis; in Milano the algorithm automatically assigned spouses to the same arm of the trial. In Arezzo, Rimini, and Torino, a cluster randomization was adopted, with the unit of randomization being the physician. In these centers, general practitioners were stratified according to the proportion of eligible respondents and then randomized in a 1 : 1 ratio within each class of response rate (ranging from 5% to 35%), based on a computer-generated random number sequence.

Subjects assigned to the control group were not contacted. Subjects assigned to the intervention group were sent a personal invitation letter, signed by their physician (or by the study coordinator, if the physician refused), with a prescheduled appointment for a sigmoidoscopy. A leaflet containing a brief description of the procedure and mentioning its possible side effects was also included. Recipients were asked to call the screening center to confirm, reschedule, or cancel their appointment. Those who agreed to a test date were asked to visit their physician or the screening center to obtain an enema kit. A reminder letter was mailed to all individuals who did not respond to the first invitation letter. In Rimini and Torino, a second invitation was sent to those who did not respond to the first invitation and to the reminder after 12 months.

Screening Procedure

Screening was undertaken by specialist gastroenterologists in hospital endoscopy units. Bowel preparation was limited to a single enema (133 mL of 22% sodium phosphate) that subjects were asked to self-administer at home 2 hours before the test. No dietary restriction was recommended. All patients gave written informed consent for the screening procedure before it was done. A 140-cm colonoscope was used in all centers except Genova, where a sigmoidoscope was used. The aim of the examination was to advance the endoscope beyond the sigmoid-descending colon junction under adequate bowel preparation. No sedation was offered, but it could be administered if the endoscopist thought it was necessary. The endoscopist recorded on a standard form information about adequacy of bowel preparation, reach of the scope, characteristics of detected lesions, visualization of other findings, and occurrence of immediate complications. If the sigmoidoscopy could not be performed because of inadequate bowel preparation, the screenee was invited to repeat the test at a later date.

After the examination, the endoscopist gave each patient a letter explaining the results and reminding the patient of the limitations of the procedure already mentioned in the leaflet. Individuals were advised to contact their physician or the endoscopy unit if they noticed rectal bleeding or experienced abdominal pain during the first few days after the procedure. Immediately after the exam, all screenees were asked to complete a short questionnaire administered by a research assistant independent of the endoscopy staff, asking about the degree of pain and embarrassment experienced during the test. Patients were asked by the interviewer to indicate which of four mutually exclusive statements best described their experience of pain: only mild discomfort; I thought it would be worse; I hope it will not be necessary to repeat the test again; it was the most severe pain I have ever experienced. Embarrassment was also rated on a four-level scale: unacceptable, severe, moderate, mild.

Management of Polyps and Referral for Colonoscopy

The study protocol stipulated that polyps 5 mm or smaller should be removed during sigmoidoscopy, using the cold snare technique *(19–20).* Diathermy snare was not recommended because it has been associated with an increased risk of complications *(21–22)* and because the heating effect of electrocoagulation may render the specimens difficult to examine *(20).* Screenees who had one distal polyp larger than 5 mm, or inadequate bowel preparation and at least one polyp, or invasive colorectal cancer were referred for colonoscopy. In a few cases the referral to colonoscopy was made by the endoscopist, based on his or her clinical judgement. Any removed polyp was analyzed by histologic examination. Colonoscopy was also indicated, on the basis of histologic examination of small polyps ($\leqslant$5 mm) excised at sigmoidoscopy, for subjects with three or more adenomas, with one villous or tubulovillous adenoma [villous component >20% *(23)*], or with one adenoma with severe dysplasia. When the colonoscopy could not be completed due to patient discomfort, a double-contrast barium enema was indicated; when that could not be achieved due to unsatisfactory bowel preparation the patient was invited to undergo a repeat colonoscopy within 6 months.

Criteria for colonoscopic surveillance. A follow-up colonoscopy was scheduled at 3 years for all patients who, after being referred for colonoscopy, were found to have colorectal cancer or "high-risk" adenomas (i.e., one adenoma of $\geqslant$10 mm an adenoma with severe dysplasia, an adenoma with villous component >20%, or three or more adenomas of any type). Subjects with negative sigmoidoscopy or with other types of polyps were discharged and offered no further follow-up.

Histologic evaluation. Polyps and cancers were classified according to World Health Organization criteria *(23).* Cancer was defined as the invasion of malignant cells beyond the muscularis mucosae. To avoid inappropriate bowel surgery, slides of malignant adenomas were reviewed by two pathologists (a consensus diagnosis was reached in case of discordance) to assess features associated with low risk of lymph nodal metastases *(24)* (i.e., low-grade, well, or moderately differentiated lesions; resection margin free of cancer; neoplastic embolization absent). In addition, slides of all cancers and of a sample of adenomas with severe dysplasia were reviewed blindly by one pathologist from the U.K. group that was conducting the parallel flexible sigmoidoscopy screening trial (Professor G. Williams), and one pathologist from the Italian group (Dr. M. Risio). The classification of discordant cases was based on the majority diagnosis including the original diagnosis.

Statistical Analysis

Polyp size was classified according to the diameter of the largest polyp recorded by the endoscopist. For the statistical analysis the largest or the most advanced polyp detected in each individual was used. Polyps detected at screening sigmoidoscopy, including those lesions located beyond the sigmoid-descending colon junction, were defined as distal polyps.

A complete colonoscopy was reported if the cecum could be visualized or, in the case of failure, when a second colonoscopy performed within 6 months of the previous one was able to visualize the cecum. The combined results of the two colonoscopies were included in the analysis. Data concerning the performance of colonoscopy, in terms of completion rate and complications, are reported only for those examinations performed before cancer surgery because colonoscopies performed after bowel resection may be influenced by clinical and technical factors that are not directly relevant to a screening context.

Chi-square tests were used to test for statistical significance in comparisons of proportional parameters. Relative risks (RRs) with 95% confidence intervals (CIs) computed on the basis of the normal approximation of the log (RR) distribution using the Taylor series-derived variance of log (RR) *(25)* were calculated to estimate differences in the characteristics of detected lesions by sex and age. All statistical tests were two-sided and were considered statistically significant at $P<.05$. In this interim report, we did not adjust for the hybrid randomization design in the statistical analysis. As a consequence, the actual P values and 95% CIs may be slightly larger than those presented here. However, the differences are likely to be small, given the large number of clusters and their small size.

We planned to enroll 40 000 eligible respondents and to achieve an attendance rate of about 70% in the screening arm. Assuming the age-specific incidence rates for the period 1988–1992, as reported in the local cancer registries *(26),* and a weighted lead time of screen-detected colorectal cancer (weighted average) of 3.5 years, the targeted sample size would give 80% power to detect a 21% reduction in incidence of colorectal cancer in the intervention group at 6 years that is statistically significant at the 5% level using a one-sided test *(27).* A statistically significant reduction in mortality cannot be detected before 11 years of follow-up.

RESULTS

Recruitment and Interest-in-Screening Questionnaire

We mailed the interest-in-screening questionnaire to 236 568 people, of whom 56 532 (23.9%) replied (Fig. 1). Of the 43 010 (18.2%; range 14.8%–24.8% in the six trial centers) respondents who said they would definitely or probably attend screening if offered it, 4838 (11.2%) were found to be ineligible. Of the 13 522 respondents who said they were not interested, 1244 (9.2%) were found to be ineligible (Fig. 1). In total, 34 292 people were assigned randomly to one of the two arms (Fig. 1). Cluster randomization (i.e., by physician) was used in three centers contributing 17 602 patients from the rosters of 507 physicians; the remaining 16 690 patients were randomized individually. Recruitment began in October 1995 and was completed in April 1999.

Characteristics of subjects assigned to the intervention and to the control arm (Table 1) were estimated to evaluate the balance of randomization. Age and sex were well balanced between the intervention and control arms, as were family history of colorectal cancer and interest in screening. The proportion of people who had a colorectal endoscopy (colonoscopy or sigmoidoscopy) in the past 3–25 years was higher in the intervention arm than in the control arm (8.6% versus 7.9%).

Compliance and Management of Trial Participants

Of the 17 148 subjects randomly assigned to the intervention arm, 9999 (58.3%) actually attended the endoscopy unit to receive a sigmoidoscopy exam (Fig. 1). Of the 9558 subjects who indicated in the interest-in-screening questionnaire that they would definitely have the test if invited, 6713 (70.2%) attended; of the 7590 who responded that they would probably have the test if invited, 3286 attended (43.3%) ($P<.001$).

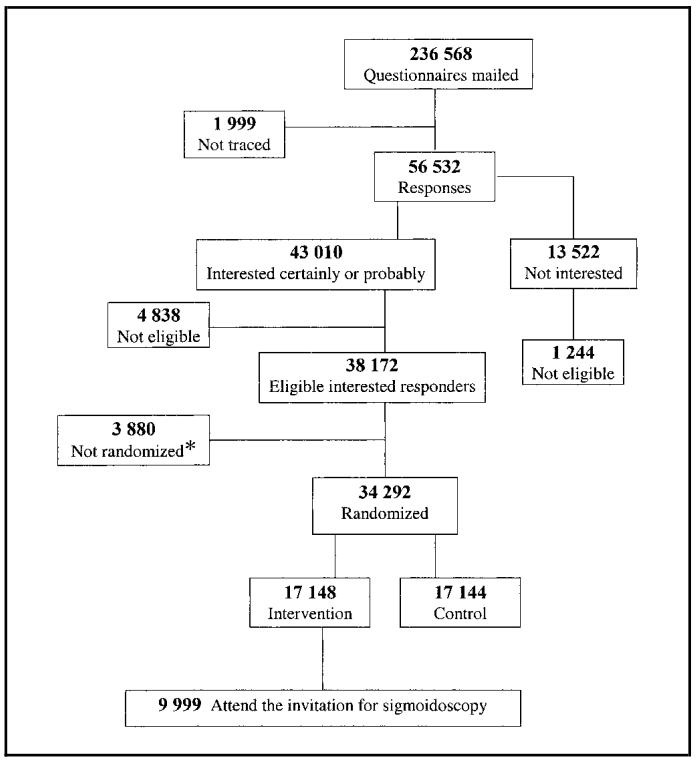

Fig. 1. Trial flow diagram. *Because of the low compliance observed in Genova during the initial recruitment period among subjects who responded that they would probably have the test if invited, they were no longer randomized at this center beginning in December 1996.

Table 1. Characteristics of the study population

Characteristic	N (%) Intervention N = 17 148	N (%) Control N = 17 144
Sex		
Men	8576 (50.0)	8658 (50.0)
Women	8572 (50.0)	8586 (50.0)
Age at randomization		
55–59	9574 (55.8)	9676 (56.4)
60–64	7574 (44.2)	7468 (43.6)
Interest in screening		
Definitely yes	9558 (55.7)	9517 (55.5)
Probably yes	7590 (44.3)	7627 (44.5)
Family history of colorectal cancer*		
Negative	15 247 (88.9)	15 321 (89.4)
Positive	1901 (11.1)	1823 (10.6)
Colorectal endoscopy in the past†		
No	15 666 (91.4)	15 791 (92.1)
Yes	1482 (8.6)	1357 (7.9)

*One first-degree relative with colorectal cancer (people with ⩾2 first-degree relatives with colorectal cancer were excluded from randomization.

†Colorectal endoscopy, sigmoidoscopy, or colonoscopy performed between 3 and 25 years before study entry.

Attendance rates in the different centers, except for Genova, ranged from 54.3% to 64.1%. Overall attendance in Genova (65.5%) was higher than in the other centers because, starting in December 1996, only subjects who responded that they would definitely have the test if invited were randomized at that center. Indeed, low compliance was observed in Genova during the initial recruitment period among subjects who responded that they would probably have the test if invited; therefore, such subjects were no longer randomly assigned. The second invitation, which was mailed after 12 months to subjects who did not respond to the first invitation and to the mailed reminder, resulted in a 5.8% absolute increase in the attendance rate in Rimini and Torino.

The sigmoidoscopy could be completed (i.e., reached beyond the sigmoid-descending colon junction, under adequate bowel preparation) on a single occasion in 7977 (79.8%) of the 9999 attenders. Among the remaining 2022 subjects, the examination was terminated because of pain or bowel adhesions in 749 subjects (37.0%), and unsatisfactory bowel preparation resulted in only partial visualization of the colonic mucosa in another 650 subjects (32.1%). Of these 1399 (749 + 650) patients, 119 were referred for colonoscopy because a polyp was detected in the segments examined and the other 1280 subjects were not asked to return for subsequent tests. The other 623 subjects (30.8%) had bowel preparation that was so inadequate that no segment of the bowel mucosa could be visualized; these subjects were all offered new tests, and 535 (85.9%) attended. The examination was completed to the descending colon in 468 of these individuals. Therefore, a complete sigmoidoscopy to the distal descending colon was achieved in 8445 (7977 + 468) of the 9999 attenders (84.5%).

Out of 9999 screenees, 9911 (7977 + 749 + 650 + 535) were actually examined, and 88 were not. Of the 9911 subjects who were examined, there was no evidence of pathology in 8166 (82.4%) (Fig. 2). For 152 additional subjects, a tissue specimen (⩽5 mm) was removed and classified by the pathologist as normal for 96 subjects; the tissue was missed or the sample was inadequate in the other 56 subjects. Another 741 subjects had low-risk polyps 5 mm or smaller (i.e., a hyperplastic polyp in 306 subjects and a tubular adenoma in 435 subjects). An additional 20 patients (19 with clinical evidence of colorectal cancer and one following perforation) were referred for surgery immediately after sigmoidoscopy. The remaining 832 subjects were referred for colonoscopy, and 775 (93.1%) of those attended (Fig. 2). In 638 of the 832 subjects (Fig. 3), the colonoscopy was indicated based on the characteristics of distal polyps; in 119 cases, referral for colonoscopy followed detection of a small polyp during an incomplete sigmoidoscopy (this policy was adopted to avoid a third endoscopic procedure—colonoscopy—in those people in whom high-risk polyps were detected at the second sigmoidoscopy); and in 75 cases, referral was based on the clinical judgement of the endoscopist (e.g., presence of five or more hyperplastic polyps, blood in the lumen of the intestine, patients' self-reported worry about abdominal symptoms, family history of colorectal cancer, concern about safety of polypectomy for patients on anticoagulants).

Among the 775 patients who had a colonoscopy, the examination could not be completed to the cecum in 188 patients (24.3%). Of these 188 patients (Fig. 3), 14 had a repeat colonoscopy within 12 months, 76 underwent a double-contrast barium enema, one required surgery following perforation, and 17 refused further investigation; no further assessment was recommended for the remaining 80 patients. Overall, therefore, only 17 patients of the 775 who had received colonoscopy were not adequately assessed (Fig. 3). A subsequent surveillance colonoscopy (Fig. 2) was indicated for 395 subjects (357 with high-risk adenomas, 27 with low-risk distal adenomas who harbored polyps in the proximal colon that could not be recovered for histologic examination, and 11 with colorectal cancer treated

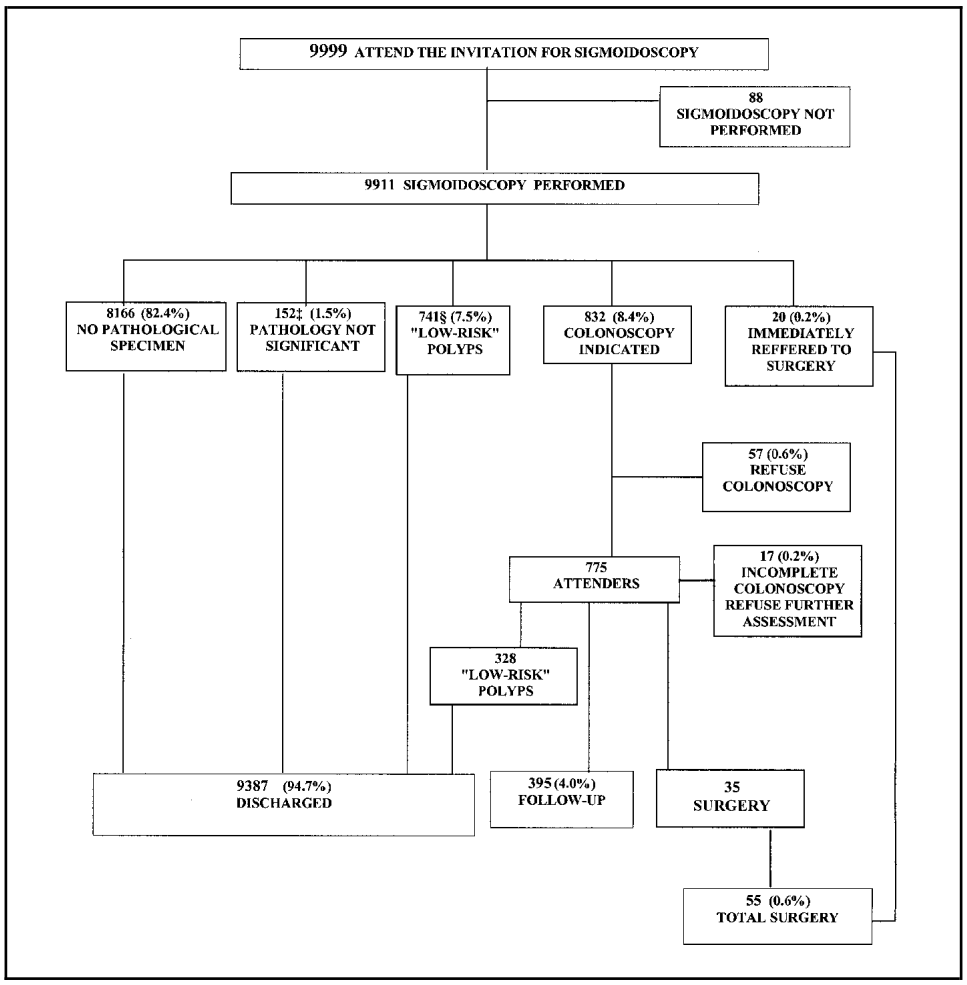

Fig. 2. Management of trial participants.

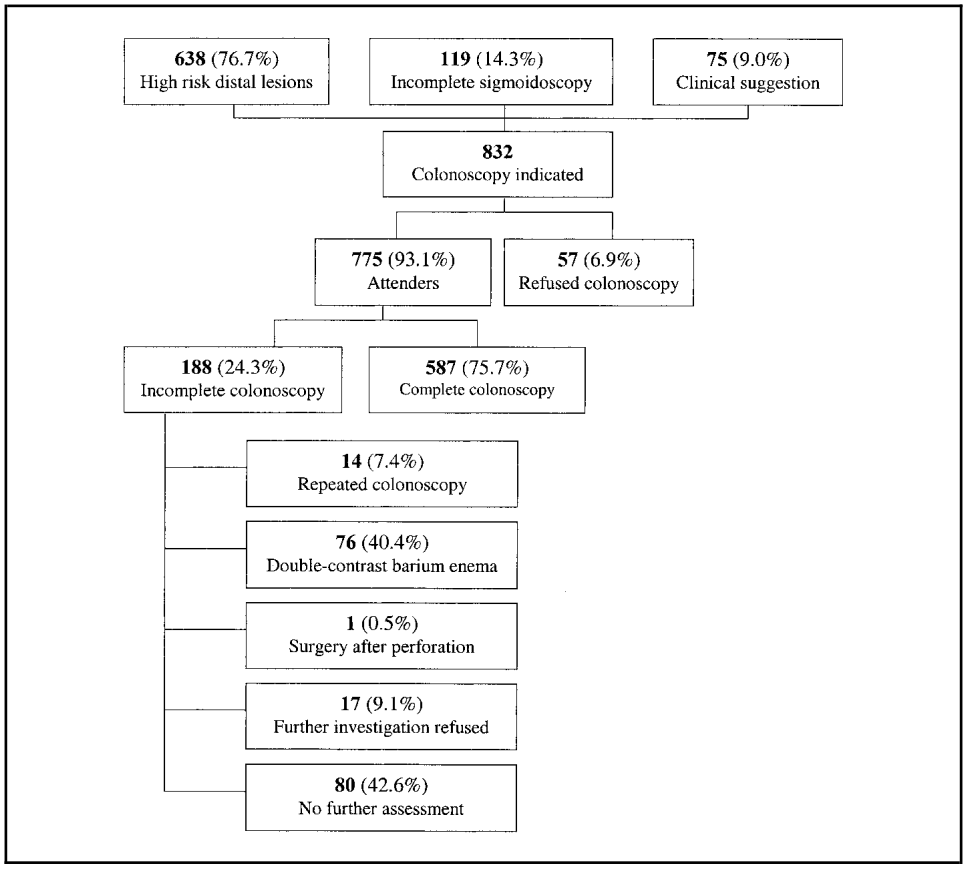

Fig. 3. Trial profile showing indication to colonoscopy after screening sigmoidoscopy, and management of subjects who received colonoscopy.

by endoscopic excision); no further assessment was necessary for 328 subjects (264 with low-risk polyps, 62 with pathology deemed not clinically significant, and two with negative endoscopy who had been referred for colonoscopy based on family history or detection of blood in the distal colon); and surgery was indicated for 35 subjects (17 with distal colorectal cancer, seven with proximal colorectal cancer, 10 with adenomas that were deemed to be too large for endoscopic excision, and one following perforation).

Yield of Benign Lesions

The prevalence of distal polyps among the 9911 subjects who received sigmoidoscopy was 17.6%. Multiple polyps were detected in 477 (4.8%) subjects (279 had two polyps, and 198 had three or more). Distal adenomas were detected in 1070 (10.8%) subjects (range, 5.9%–14.7% across the trial centers) (Table 2). Men showed a statistically significantly higher prevalence than women of non-neoplastic polyps (RR = 2.08, 95% CI = 1.71 to 2.53), adenomas (RR = 1.64, 95% CI = 1.46 to 1.85), and colorectal cancer (RR = 2.30, 95% CI = 1.22 to 4.36). Distal adenomas were detected more frequently among subjects 60 years of age and older than among those younger than 60 years (RR = 1.15, 95% CI = 1.03 to 1.29). Subjects 60 years of age and older also showed a higher prevalence of advanced adenomas (⩾10 mm, with villous component >20%, or with high-grade dysplasia) than those younger than 60 years (RR = 1.28, 95% CI = 1.04 to 1.58). The proportion of adenomas with severe dysplasia or with villous component greater than 20% also increased with polyp size: it was 9.8% for adenomas smaller than 10 mm and 45.8% ($P<.001$) for adenomas 10 mm or larger.

Among the 775 subjects who underwent colonoscopy, the pathologic examination diagnosed a (distal) cancer in 28 subjects. They were referred to colonoscopy, according to the criteria previously described, because at sigmoidoscopy distal lesions, without a manifest clinical appearance of cancer, were detected. Among the 747 subjects without distal cancer (Table 3), proximal polyps were detected in 174 (23.3%), 116 of whom were found to have adenomas (range, 3.5%–21.6% across the trial centers). Men were twice as likely as women to have advanced adenomas in the proximal colon (RR = 2.3, 95% CI = 0.9 to 7.0). No association of pathology with age was observed for proximal lesions.

Screen-Detected Cancers

There were a total of 54 subjects with colorectal cancer (Table 4): 47 with a distal cancer, identified among the 9911 subjects who underwent sigmoidoscopy (19 immediately referred for surgery and 28 referred for colonoscopy), and seven among the 747 patients without distal cancer who were referred for colonoscopy. One patient with distal colorectal cancer also harbored a synchronous malignant lesion in the proximal colon, another harbored two tumors in the sigmoid colon, and a third had two tumors at the splenic flexure. Thus, together these patients contained 57 malignant colorectal tumors: 48 were detected at sigmoidoscopy (18 in the rectum, 28 in the sigmoid colon, and two in the descending colon), and nine were detected at colonoscopy (three at the splenic flexure, one in the transverse colon, one at the hepatic flexure, three in the ascending colon, and one in the cecum). Twenty-six of the colorectal cancers were malignant adenomas. The detection rate for colorectal cancer was 5.4 per 1000 (54/9911), and for 29 of the 54 patients (54%) the colorectal cancer was classified as Dukes' A or was judged to be localized. Indeed, treatment was limited to endoscopic excision in 11 of 26 cases of malignant adenomas.

Serious Adverse Events of Screening

Three people developed complications requiring hospitalization. Among the 9911 subjects who underwent sigmoidoscopy there was one perforation (0.1 per 1000), and among the 775 subjects who underwent colonoscopy there was one perforation and one episode of bleeding following polypectomy (both 1.3 per 1000). In addition, one patient was brought to an emergency room with a peritonitis-like reaction the day after screening sigmoidoscopy, although his symptoms disappeared within a few hours; two patients developed glutaraldehyde colitis; one patient had an allergic reaction to latex gloves; two patients, both receiving anti-epileptic treatment, suffered seizures that required medical treatment; 17 patients had self-limited bleeding following polypectomy (10 at sigmoidoscopy and seven at colonoscopy); 49 patients complained of mild vagal reactions (nausea, feeling faint, or feeling dizzy) (42 at sigmoidoscopy and seven at colonoscopy); and 24 patients (eight at sigmoidoscopy and 16 at colonoscopy) complained of abdominal pain. Overall, minor self-limited complications occurred in 0.6% (60/9911) of patients who had sigmoidoscopy and in 4% (30/775) of patients who received colonoscopy.

Patients' Experience

Of the 9911 people who underwent sigmoidoscopy, 9394 (94.8%) completed the short questionnaire administered immediately after the test. Of these, 60.4% reported mild discomfort

Table 2. Characteristics of screen-detected lesions in the distal colon by sex and age

Characteristic	N (%)				
	Total	Men	Women	Age 55–59	Age 60–64
No polyp	**8169 (82.4)**	**4112 (78.0)**	**4057 (87.4)**	**4338 (82.9)**	**3831 (81.9)**
Missed polyp or inadequate sample	110 (1.1)	69 (1.3)	41 (0.9)	56 (1.1)	54 (1.2)
Normal mucosa	128 (1.3)	91 (1.7)	37 (0.8)	66 (1.3)	62 (1.3)
Hyperplastic polyp	387 (3.9)	267 (5.1)	120 (2.6)	219 (4.2)	168 (3.6)
Non-neoplastic polyp	**515 (5.2)**	**358 (6.8)**	**157 (3.4)**	**285 (5.5)**	**230 (4.9)**
Tubular and low-grade dysplasia and size <10 mm	729 (7.4)	457 (8.7)	272 (5.9)	368 (7.0)	361 (7.7)
Villous component >20% or high-grade dysplasia and size <10 mm	79 (0.8)	54 (1.0)	25 (0.5)	36 (0.7)	43 (0.9)
Tubular and low-grade dysplasia and size ⩾10 mm	142 (1.4)	99 (1.9)	43 (0.9)	72 (1.4)	70 (1.5)
Villous component or high-grade dysplasia and size ⩾10 mm	120 (1.2)	86 (1.6)	34 (0.7)	51 (1.0)	69 (1.5)
Any adenoma	**1070 (10.8)**	**696 (13.2)**	**374 (8.1)**	**527 (10.1)**	**543 (11.6)**
Cancer	**47 (0.5)**	**34 (0.6)**	**13 (0.3)**	**25 (0.5)**	**22 (0.5)**
Total screened	**9911**	**5269**	**4642**	**5231**	**4680**

Table 3. Number (%) of people with polyps or cancer detected in the proximal colon* and relative risks for men as compared with women

Characteristic	N (%)			
	Total	Men	Women	RR (95% CI)†
Underwent colonoscopy	747	509	238	
Any polyp	174 (23.3)	129 (25.3)	45 (18.9)	**1.3** (1.0–1.8)
Adenomas	116 (15.5)	86 (16.9)	30 (12.6)	**1.3** (0.9–2.0)
⩾3 adenomas	21 (2.8)	14 (2.8)	7 (2.9)	**0.9** (0.4–2.3)
Tubulo-villous/villous histology severe dysplasia‡	27 (3.6)	24 (4.7)	3 (1.3)	**3.7** (1.1–12.3)
Cancers	7 (0.9)	6 (1.2)	1 (0.4)	**2.8** (0.3–23.2)
Advanced pathology§	35 (4.7)	29 (5.7)	6 (2.5)	**2.3** (0.9–7.0)

*Excluding the 47 patients with a distal cancer, identified among the 9911 subjects undergoing sigmoidoscopy (19 immediately referred to surgery and 28 referred for colonoscopy).

†Relative risk (95% confidence interval [CI]) for men compared with women.

‡Most advanced lesion in subject.

§Any of the following confirmed after pathological analysis of specimens: adenoma 10 mm or larger, tubulo-villous or villous histology, severe dysplasia.

Table 4. Number of patients with colorectal cancer according to method of treatment, Dukes' stage and TNM* status

Treatment	Total†		T status			N status				M status	
	n	%	T1	T2	T3	N0	N1	N2	Nx	M0/Mx	M1
Endoscopic excision	11	(20.4)	11	0	0	0	0	0	11	11	0
Local excision	1	(1.9)	1	0	0	0	0	0	1	1	0
Open abdominal surgery											
Dukes' A	17	(31.5)	13	4	0	13	0	0	4‡	17	0
Dukes' B	9	(16.7)	0	0	9	9	0	0		9	0
Dukes' C	14	(25.9)	1	0	13	0	10	2	2§	14	0
Dukes' D	2	(3.7)	0	0	2	0	0	2	0	0	2
Total	54	(100)	26	4	24	22	10	4	18	52	2

*TNM = tumor–node–metastasis.

†Two men and one woman were detected with two synchronous colorectal cancers, and only one cancer for each is shown on the Table. One man had two Dukes' C cancers in the sigmoid colon (one pT3, N1, M0; one pT2, N1, M0, not included in the table); one man had two Dukes' C cancers at the splenic flexure (both pT3, N2, M1; only one included in the table); one woman had a Dukes' C cancer in the sigmoid colon, treated by anterior resection (pT2, N1, M0, not included in table) and a Dukes' C cancer at the hepatic flexure (pT3, N1, M0; included in the table).

‡Fewer than five nodes were examined; all were negative.

§Fewer than 12 nodes were examined; one, two, or three were positive.

and 22.9% reported that they found the test to be less painful than expected. Only 2.0% described the pain as the most severe they had ever experienced. Women rated the pain as severe ("I hope it will not be necessary to repeat the test again" or "It was the most severe pain I have ever experienced") more often than men (16.0% versus 7.6 %; $P<.001$). Only 5.1% of the screenees found the test more than mildly embarrassing. This proportion was similar for men and women.

Discussion

We report the baseline results of a large multicenter randomized trial of sigmoidoscopy screening conducted in Italy. The attendance rate among subjects assigned to the screening arm was 58.3%. Distal adenomas were detected in 10.8% (1070/9911) of those receiving sigmoidoscopy. The yield of proximal adenomas among those without distal cancer who underwent colonoscopy was 15.5% (116/747). The detection rate for colorectal cancer was 5.4 per 1000 (of which 54% of the cases were Dukes' A or localized).

The trial protocol was similar to the one adopted in the U.K. trial *(17).* The main differences concerned the randomization procedure and the criteria for colonoscopy referral. Cluster randomization (i.e., using the physician as the unit of randomization) was adopted in three of the six Italian centers to reduce the probability of contamination in a context of open-access (i.e., through the physician) endoscopy. In the U.K. trial *(17),* a household-based randomization procedure was adopted.

The criteria for colonoscopy referral were the same in the Italian and U.K. trials, except for the size of distal polyps and the management of subjects with distal polyps detected at incomplete sigmoidoscopy. In Italy, all subjects with distal polyps larger than 5 mm were referred for colonoscopy to increase the sensitivity of screening for advanced proximal neoplasia, whereas in the United Kingdom only patients with distal polyps larger than 10 mm were referred for colonoscopy. If the same criteria for "high-risk" distal lesions had been adopted in Italy as in the United Kingdom, 486 of the 9911 screenees (4.9%) would have been referred for colonoscopy, instead of 832 (8.4%). Approximately 49% of this 3.5% difference (i.e., 171 subjects) is attributable to the different threshold of polyp size. Also, the Italian trial, but not the U.K. trial, included the option of referring people with incomplete sigmoidoscopy for colonoscopy when detecting any distal polyp, and this difference accounted for about 34% of the additional referrals. In the remaining Italian cases, referral for colonsocopy was based, as in the U.K. trial, on the judgement of the endoscopist. Thus, adopting the 10-mm size threshold would have resulted in 171 fewer colonoscopy referrals at baseline. Of these 171 patients, 155 underwent colonoscopy, and advanced proximal lesions were detected in three (1.9%). This prevalence is similar to that among men and

women without distal polyps who underwent colonoscopy screening *(39).* By contrast, advanced neoplasms were found in the proximal colon in 9.9% of patients with "high-risk" (according to the criteria adopted in the U.K. trial) distal adenomas. Therefore, the lower threshold size for distal adenomas used in the Italian trial does not appear to have considerably increased the sensitivity for "high-risk" proximal polyps.

The two-stage recruitment procedure used in all centers in the Italian trial (i.e., questionnaire to assess interest in and eligibility for screening followed by randomization of interested and eligible respondents) increased the attendance rate, which was about 58%, double the 29% uptake rate observed in a pilot study in Torino *(28).* However, although this approach increased the study efficiency, it decreased the degree of coverage of the target population, at least as compared with the pilot study. The 58% attendance rate among the 16% of eligible respondents who expressed an interest in screening resulted in the enrollment of about 9% of the source population.

We cannot exclude the possibility that these response rates reflect self-selection of subjects who might have a risk of colorectal cancer different from that in the general population. Analyses of people recruited in Torino and Genova (data not shown) indicate that people with higher levels of education had a higher response rate to the questionnaire than people with lower levels of education. A higher incidence of colorectal cancer has already been documented in people with higher levels of education compared with people with lower levels of education *(29).* However, this selection process should not affect the validity of the trial, because only eligible responders were entered into the trial. Also, there is no apparent biologic reason for the proportional benefit of screening to be different among subjects who have different risks of colorectal cancer.

Because all subjects targeted for recruitment will be followed up for colorectal cancer incidence and mortality through regional registries of hospital discharge records, death certificates, and local cancer registries, we will be able to compare baseline risks of colorectal cancer among those who did not respond to the mailed questionnaire with risks among those who were allocated to the control group of the trial. Therefore, we will be able to assess the impact of the low response rate to the questionnaire (23.9%) on the generalizability of the trial findings. Moreover, because the response rate to the mailed questionnaire was similar to the observed attendance rate in the pilot phase of the trial *(28),* respondents are likely to be representative of the individuals who would participate in a colorectal cancer screening program in Italy.

It should also be noted that no mass-media campaign could be implemented in the trial context, which may partially explain the low response rate to the questionnaire. However, the cumulative response rate may be more relevant for evaluating the impact of a screening strategy based on a single test than compliance with each single invitation. The 5.8% absolute increase in the proportion of attenders observed in two trial centers (Rimini and Torino) following an additional invitation mailed to nonresponders after 1 year indicates that repeated invitations might represent an effective strategy to extend population coverage.

The high detection rate for colorectal cancer may be partially attributable to the selective enrollment of a high proportion of subjects who are at increased risk for the disease. However, it might also reflect the magnitude of the anticipation of the cancer diagnosis achievable through sigmoidoscopy. Walter and Day *(31)* suggest that the ratio of prevalence to incidence can be considered an estimate of the mean sojourn time. Based on the observed prevalence in the trial and on incidence data available from the cancer registries in the study areas *(30),* we estimate this ratio to be 4.6, suggesting that, in general, the approach adopted by the SCORE trial for colorectal cancer screening (sigmoidoscopy and total colonoscopy for subjects with high-risk distal adenomas) detects many early-stage malignant lesions. The high proportion of malignant adenomas, which made up 26 of the 54 (48%) screen-detected colorectal cancers in our study, supports this hypothesis.

The observed detection rate is consistent with those seen in studies comparing sigmoidoscopy and fecal occult blood testing *(32–34).* Moreover, the detection rate of adenomas 10 mm or larger or with a villous component of more than 20% (3.7%) was approximately four times higher than in studies of fecal occult blood testing screening (using either guaiac or immunochemical tests) *(35–37).* This finding is consistent with the expected impact of screening on colorectal cancer incidence because the estimated conversion rate of these lesions is high *(13,38).*

The need to repeat sigmoidoscopy in cases of unsatisfactory bowel preparation is a crucial problem because of the possibility of undetected lesions and the unwillingness of most patients to undergo a second sigmoidoscopy examination. About half of the subjects with incomplete sigmoidoscopy due to unsatisfactory bowel preparation were not invited to repeat the test. It appears that physicians offered a repeat sigmoidoscopy examination only when the reach of the instrument was so limited that they could not be confident that important lesions had not been missed. Indeed, the median reach of the instrument in these cases was 45 cm, and no lesion was detected in the segments examined (data not shown). Moreover, some patients may well have been unwilling to repeat the whole screening procedure. In our pilot study (28), about two thirds of subjects with inadequate bowel preparation who were offered a new test date did not attend.

Colonoscopy could not be completed to the cecum in about 25% of the patients. The lower completion rate in our screening setting, as compared with that reported in other studies *(33,40),* may be explained by a different attitude of the doctors and patients in our study. To minimize the risk associated with the procedure, the endoscopists participating in our study tended to avoid administering sedation and to interrupt the examination if patients complained of excess pain. That this approach likely did not lead to missed cancers seems to be supported by the fact that no proximal neoplasms were detected among the 76 patients with incomplete colonoscopy who underwent a double-contrast barium enema. On the other hand, asymptomatic patients may have been less motivated to tolerate procedure-related disturbances.

The acceptability of sigmoidoscopy was satisfactory, with only 2% of the screenees rating the pain associated with the procedure as severe, although the test was routinely performed without sedation. Overall, minor, self-limited complications occurred in about 0.6% of the subjects who received sigmoidoscopy and about 4% of those who received colonoscopy. The rates of severe complications compare favorably with those observed in other studies of both examinations *(41–45),* especially given that 89% of the subjects in our trial who underwent colonoscopy had at least one polyp removed (data not shown). A recent prospective study *(46)* suggested that the previous reports, which were based mainly on patient record reviews, might have

underestimated the complication rate. In that study, only 15% of the complications reported by patients interviewed 30 days after outpatient colonoscopy were known before the interview. Immediate complications were systematically recorded in our study for all patients before they left the endoscopy unit. Information on late complications was obtained from physician and endoscopist reports and by directly contacting all patients referred for surveillance. We cannot exclude the possibility that, in some cases, additional minor complications that did not require hospitalization or referral to hospital outpatient clinics occurred in the days following screening.

A high variability was observed across the trial centers, when considering a series of performance indicators (e.g., completion rates of sigmoidoscopy and colonoscopy—which ranged from 81.5% to 98.2% and from 51.8% to 87.1%, respectively—and detection rates of distal and proximal adenomas, which ranged from 5.9% to 14.7% and from 3.5% to 21.6%, respectively). This variability suggests the need to implement quality-control procedures when planning to use sigmoidoscopy in a large-scale, population-based screening program. Minimum performance standards of endoscopic examinations should be established to achieve adequate levels of accuracy from these screening procedures.

In conclusion, the baseline results from the SCORE trial show that sigmoidoscopy can be an acceptable and safe screening strategy for colorectal cancer. The high yield of advanced lesions and early colorectal cancer is consistent with the projected substantial impact of sigmoidoscopy screening on colorectal cancer incidence and mortality. The positive experience reported by attenders may contribute to enhance participation rates of screening programs in the future.

APPENDIX

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REFERENCES

(1) Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 1999;83:18–29.

(2) ISTAT. Istituto Nazionale di Statistica (National Statistical Institute) [Last accessed 10/1/2002] (Available at: htpp://www.istat.it).

(3) Capocaccia R, De Angelis R, Frova L, Gatta G, Sant M, Micheli A, et al. Estimation and projections of colorectal cancer trends in Italy. Int J Epidemiol 1997;26:924–32.

(4) Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 1995;123:904–10.

(5) Kavanagh AM, Giovannucci EL, Fuchs CS, Colditz GA. Screening endoscopy and risk of colorectal cancer in United States men. Cancer Causes Control 1998;9:455–62.

(6) Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas . N Engl J Med 1992; 326:658–62.

(7) Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977–81.

(8) Thiis-Evensen E, Hoff GS, Sauar J, Langmark F, Majak BM, Vatn MH. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark Polyp Study I. Scand J Gastroenterol 1999;34: 414–20.

(9) Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992;326:653–7.

(10) Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality . J Natl Cancer Inst 1992;84:1572–5.

(11) Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603–7.

(12) Morson BC. Evolution of cancer of the colon and rectum. Cancer 1974;34(Suppl):845–9.

(13) Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. Gastroenterology 1987;93: 1009–13.

(14) Kronborg O, Fenger C. Clinical evidence for the adenoma-carcinoma sequence. Eur J Cancer Prev 1999;8(Suppl 1):S73–86.

(15) Atkin WS, Cuzick J, Northover JM, Whynes DK. Prevention of colorectal cancer by once-only sigmoidoscopy. Lancet 1993;341:736–40.

(16) Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, editors. Cancer incidence in five continents. Vol. VII, No.143. Lyon (France): IARC Scientific Publications; 1997.

(17) Atkin WS, Edwards R, Wardle J, Northover JM, Sutton S, Hart AR, et al. Design of a multicenter randomized trial to evaluate flexible sigmoidoscopy in colorectal cancer screening. J Med Screen 2001;8:137–44.

(18) UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet 2002;359:1291–1300.

(19) McAfee JH, Katon RM. Tiny snares prove safe and effective for removal of diminutive colorectal polyps. Gastrointest Endosc 1994;40:301–3.

(20) Rossini FP, Arrigoni A, Pennanzio M. Treatment and follow-up of large bowel adenoma. Tumori 1995;81(3 Suppl):38–44.
(21) Wadas DD, Sanowski RA. Complications of the hot biopsy forceps technique. Gastrointest Endosc 1988;34:32–7.
(22) Peluso F, Goldner F. Follow-up of hot biopsy forceps treatment of diminutive colonic polyps. Gastrointest Endosc 1991;37:604–6.
(23) Jass JR, Sobin LH. Histological typing of intestinal tumours. 2nd ed. Berlin (Germany): Springer; 1989.
(24) Coverlizza S, Risio M, Ferrari A, Fenoglio-Preiser CM, Rossini FP. Colorectal adenomas containing invasive carcinoma. Pathologic assessment of lymph node metastatic potential. Cancer 1989;64:1937–47.
(25) Katz D, Baptista J, Azen SP, Pike MC. Obtaining confidence intervals for the risk ratio in cohort studies. Biometrics 1978;34:469–74.
(26) Zanetti R, Crosignani P, Rosso S. Il cancro in Italia. I dati di incidenza dei Registri Tumori. Vol. 2: 1988–1992. Rome (Italy): Il Pensiero Scientifico Editore; 1997.
(27) Walter SD. Determination of significant relative risks and optimal sampling procedures in prospective and retrospective comparative studies of various sizes. Am J Epidemiol 1977;105:387–97.
(28) Senore C, Segnan N, Rossini FP, Ferraris R, Cavallero M, Coppola F, et al. Screening for colorectal cancer by once only sigmoidoscopy: a feasibility study in Turin, Italy. J Med Screen 1996;3:72–8.
(29) Faggiano F, Zanetti R, Costa G. Cancer risk and social inequalities in Italy. J Epidemiol Community Health 1994; 48:447–52.
(30) Zanetti R, Rosso S, Gafà L, Pannelli F, Conti E, editors. Il cancro in Italia. Vol. 3: 1993–1998. Rome (Italy): Il Pensiero Scientifico Editore; 2001.
(31) Walter SD, Day NE. Estimation of the duration of a pre-clinical disease state using screening data. Am J Epidemiol 1983;118:865–86.
(32) Berry DP, Clarke P, Hardcastle JD, Vellacott KD. Randomized trial of the addition of flexible sigmoidoscopy to faecal occult blood testing for colorectal neoplasia population screening. Br J Surg 1997;84:1274–6.
(33) Brevinge H, Lindholm E, Buntzen S, Kewenter J. Screening for colorectal neoplasia with faecal occult blood testing compared with flexible sigmoidoscopy directly in a 55–56 years' old population. Int J Colorectal Dis 1997;12:291–5.
(34) Rasmussen M, Kronborg O, Fenger C, Jorgensen OD. Possible advantages and drawbacks of adding flexible sigmoidoscopy to hemoccult-II in screening for colorectal cancer. A randomized study. Scand J Gastroenterol 1999; 34:73–8.
(35) Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomized study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467–71.
(36) Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomized controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–7.
(37) Castiglione G, Zappa M, Grazzini G, Mazzotta A, Biagini M, Salvadori P, et al. Immunochemical vs guaiac faecal occult blood tests in a population-based screening programme for colorectal cancer. Br J Cancer 1996;74: 141–4.
(38) Eide TJ. Risk of colorectal cancer in adenoma-bearing individuals within a defined population. Int J Cancer 1986;38:173–6.
(39) Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000;343:169–74.
(40) Levin TR, Palitz A, Grossman S, Conell C, Finkler L, Ackerson L, et al. Predicting advanced proximal colonic neoplasia with screening sigmoidoscopy. JAMA 1999;281:1611–7.
(41) Robinson RJ, Stone M, Mayberry JF. Sigmoidoscopy and rectal biopsy: a survey of current UK practice. Eur J Gastroenterol Hepatol 1996;8:149–51.
(42) Waye JD, Kahn O, Auerbach ME. Complications of colonoscopy and flexible sigmoidoscopy. Gastrointest Endosc Clin N Am 1996;6:343–77.
(43) Anderson ML, Pasha TM, Leighton JA. Endoscopic perforation of the colon: lessons from a 10-year study. Am J Gastroenterol 2000;95: 3418–22.
(44) Gibbs DH, Opelka FG, Beck DE, Hicks TC, Timmcke AE, Gathright JB Jr. Postpolypectomy colonic hemorrhage. Dis Colon Rectum 1996;39:806–10.
(45) Garbay JR, Suc B, Rotman N, Fourtanier G, Escat J. Multicenter study of surgical complications of colonoscopy. Br J Surg 1996;83:42–4.
(46) Zubarik R, Fleischer DE, Mastropietro C, Lopez J, Carroll J, Benjamin S, et al. Prospective analysis of complications 30 days after outpatient colonoscopy. Gastrointest Endosc 1999;50:322–8.

NOTES

Support for the study was provided by a grant from the Italian Association for Cancer Research (AIRC, 1995–1997), grants from the Italian National Research Council (CNR, 95.00539.PF39 and 96.00736.PF39). The Istituto Oncologico Romagnolo (IOR), the Fondo "E Tempia," the University of Milano, and the Local Heath Unit ASL1, Torino supported the implementation of the study in Rimini, Biella, Milano, and Torino, respectively. We are grateful to Professor Geraint Williams, University of Wales College of Medicine, Cardiff, who reviewed the slides of all colorectal cancer cases and of the sample of adenomas with severe dysplasia. SOFAR s.p.a. provided the enemas for the bowel preparation. We thank Ms Frederica Gallo for editorial assistance.