DOI: 10.1093/jnci/djr284
Advance Access publication on August 18, 2011.

ARTICLE

Once-Only Sigmoidoscopy in Colorectal Cancer Screening: Follow-up Findings of the Italian Randomized Controlled Trial—SCORE

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Manuscript received February 11, 2011; revised June 28, 2011; accepted June 30, 2011.

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Background A single flexible sigmoidoscopy at around the age of 60 years has been proposed as an effective strategy for colorectal cancer (CRC) screening.

Methods We conducted a randomized controlled trial to evaluate the effect of flexible sigmoidoscopy screening on CRC incidence and mortality. A questionnaire to assess the eligibility and interest in screening was mailed to 236 568 men and women, aged 55–64 years, who were randomly selected from six trial centers in Italy. Of the 56 532 respondents, interested and eligible subjects were randomly assigned to the intervention group (invitation for flexible sigmoidoscopy; n = 17 148) or the control group (no further contact; n = 17 144), between June 14, 1995, and May 10, 1999. Flexible sigmoidoscopy was performed on 9911 subjects. Intention-to-treat and per-protocol analyses were performed to compare the CRC incidence and mortality rates in the intervention and control groups. Per-protocol analysis was adjusted for noncompliance.

Results A total of 34 272 subjects (17 136 in each group) were included in the follow-up analysis. The median follow-up period was 10.5 years for incidence and 11.4 years for mortality; 251 subjects were diagnosed with CRC in the intervention group and 306 in the control group. Overall incidence rates in the intervention and control groups were 144.11 and 176.43, respectively, per 100 000 person-years. CRC-related death was noted in 65 subjects in the intervention group and 83 subjects in the control group. Mortality rates in the intervention and control groups were 34.66 and 44.45, respectively, per 100 000 person-years. In the intention-to-treat analysis, the rate of CRC incidence was statistically significantly reduced in the intervention group by 18% (rate ratio [RR] = 0.82, 95% confidence interval [CI] = 0.69 to 0.96), and the mortality rate was non-statistically significantly reduced by 22% (RR = 0.78; 95% CI = 0.56 to 1.08) compared with the control group. In the per-protocol analysis, both CRC incidence and mortality rates were statistically significantly reduced among the screened subjects; CRC incidence was reduced by 31% (RR = 0.69; 95% CI = 0.56 to 0.86) and mortality was reduced by 38% (RR = 0.62; 95% CI = 0.40 to 0.96) compared with the control group.

Conclusion A single flexible sigmoidoscopy screening between ages 55 and 64 years was associated with a substantial reduction of CRC incidence and mortality.

J Natl Cancer Inst 2011;103:1310–1322

Several randomized controlled trials have shown that fecal occult blood testing (FOBT) in colorectal cancer (CRC) screening can reduce mortality from CRC (1). CRC incidence was also reduced in one of the trials (2), which may have resulted from endoscopic polypectomy of neoplasms in people detected with a positive test. Observational studies have shown a substantial reduction in incidence and mortality for cancer in the rectum and sigmoid colon (distal CRC) among people who had undergone endoscopy (3–6). The reduction in incidence was maintained over time suggesting that removal of adenomas at screening can indeed provide a long-term protection against development of distal CRC (3,4). Based on observational data indicating that two-thirds of CRCs arise in the rectum and sigmoid colon (7), which can be examined by flexible sigmoidoscopy, and that the prevalence of distal adenomas eventually reaches a plateau at around 60 years of age (8), a single flexible sigmoidoscopy screen offered between 55 and 64 years of age has been proposed as a suitable method for CRC screening (8). Several studies have already shown that flexible sigmoidoscopy is safe and well accepted among patients (9–12), and currently four ongoing trials are aimed at assessing the efficacy of this screening modality (9,13–15).

Results of the first 7 years of follow-up in the Norwegian trial showed a statistically significant (P = .011) reduction of CRC mortality by 59% among subjects who were screened but no reduction of CRC incidence and a non-statistically significant (P = .16) reduction in CRC mortality in the intention-to-treat analysis (14).

A statistically significant and long-lasting reduction of both incidence (P < .0001) and mortality (P < .0001) from CRC has been reported from the UKtrial after 11 years of follow-up (13).

We conducted a multicenter, randomized controlled trial in Italy to assess efficacy of flexible sigmoidoscopy screening offered once in life at 55–64 years of age ("once-only" sigmoidoscopy screening or Screening for COlon REctum [SCORE] trial), based on the UK trial protocol. We previously reported the baseline findings from the trial recruitment (9) and now report the 10-year follow-up results.

Subjects and Methods

Study Population and Recruitment

The SCORE trial (registration number ISRCTN27814061) was conducted by six trial organizing centers: Turin (with two gastroenterology units involved), Biella (one gastroenterology unit), Genoa (one gastroenterology unit), Arezzo (one gastroenterology unit), Rimini (one gastroenterology unit), and Milan (four gastroenterology units in province of Milan and two gastroenterology units in province of Como) in Italy (see "Appendix"). Approval for the study was granted by the local ethics review committees in each center. The design of the trial has been described elsewhere (9). In Arezzo, Rimini, and Turin, all patients enrolled in the rosters of a random sample of National Health Service general practitioners (GPs) were targeted for recruitment. In Milan, all patients of the GPs who volunteered to cooperate in the trial were included in the population targeted for enrollment. In Genoa and Biella, a random sample of individuals in the target age range was drawn from the National Health Service register. A total of 236568 men and women (47.7% men and 52.3% women), aged 55–64 years, included in these samples were mailed an interest-in-screening questionnaire designed to assess eligibility for and interest in screening, of whom 56532 (23.9%) responded (Figure 1). We have previously described the study protocol and reported the baseline findings of the recruitment phase of the SCORE trial (9). Responders were excluded if they reported a personal history of CRC, colorectal adenomas, or inflammatory bowel disease; having had a colorectal endoscopy within the previous 2 years; having two or more first-degree relatives with CRC; and having a medical condition that would preclude a benefit from screening.

As described in the article reporting the baseline results (9), of the 43010 (18.2%, range 14.8%–24.8%) respondents in the six trial centers who said that they certainly or probably would attend the screening if offered to them, 4838 (11.2%) were found to be ineligible. We also excluded 3880 eligible responders in Genoa from random assignment, who mentioned that they would probably be available for CRC screening, as the attendance rate was too low in that subgroup of responders (Figure 1).

Random Assignment and Invitation for Flexible Sigmoidoscopy Screening

Eligible respondents who indicated that they would "certainly" or "probably" undergo flexible sigmoidoscopy screening, if it was offered to them, were randomly allocated to intervention or control groups in the ratio 1:1. Random assignment was performed in each center by the local coordinating unit using a computer-generated allocation algorithm. In Biella, Genoa, and Milan, subjects were randomly assigned on an individual basis; in Arezzo, Rimini, and Turin a cluster randomization was adopted (the GP was the unit of randomization). GPs were stratified in classes of response rate according to the proportion of eligible respondents among their patients and then randomized in the intervention and control groups in the ratio 1:1 within each class, based on a computer-generated random numbers sequence. A total of 34292 people were randomly assigned to the intervention (N = 17148) and control (N = 17144) groups. Cluster randomization (ie, by physician) used in three centers contributed 17602 subjects from the rosters of 507 physicians; the remaining 16690 subjects were randomly assigned individually.

Subjects assigned to the control group were not contacted further. Subjects assigned to the intervention group were sent a personal invitation letter signed by their physician, with a prescheduled appointment for a flexible sigmoidoscopy screening. A leaflet

CONTEXT AND CAVEATS

Prior knowledge

After 11 years of follow-up, the UK Flexible Sigmoidoscopy Screening Trial reported long-lasting reduction of colorectal cancer (CRC) incidence and mortality by 33% and 43% respectively from CRC among screened people. A single flexible sigmoidoscopy screen offered between 55 and 64 years of age has been proposed as a suitable method for CRC screening.

Study design

A 10-year follow-up study of a multicenter randomized controlled trial conducted in Italy to assess whether flexible sigmoidoscopy screening offered once at age 55–64 years could reduce CRC incidence and mortality. The baseline findings of the trial recruitment were reported previously. Intention-to-treat and per-protocol analyses were performed to compare incidence and mortality rates in the intervention and control groups.

Contribution

The median follow-up period was 10.5 years for CRC incidence and 11.4 years for mortality (all-cause and CRC-specific mortality). In the intention-to-treat analysis, CRC incidence and mortality were reduced by 18% and 22%, respectively. The reduction in mortality was not statistically significant. However, in a per-protocol analysis, adjusted for noncompliance, CRC incidence and mortality were both statistically significantly reduced by 31% and 38%, respectively. Moreover, in the intervention group the incidence of advanced CRCs (UICC stage 3 or 4) was reduced by 27%.

Implication

Flexible sigmoidoscopy offered once at age 55–64 years is a safe and effective method for CRC screening.

Limitation

Because of a self-selection bias in trial recruitment, a longer follow-up of at least 14 years may be needed to see a 25% statistically significant reduction in mortality in the intervention group compared with the control group.

From the Editors

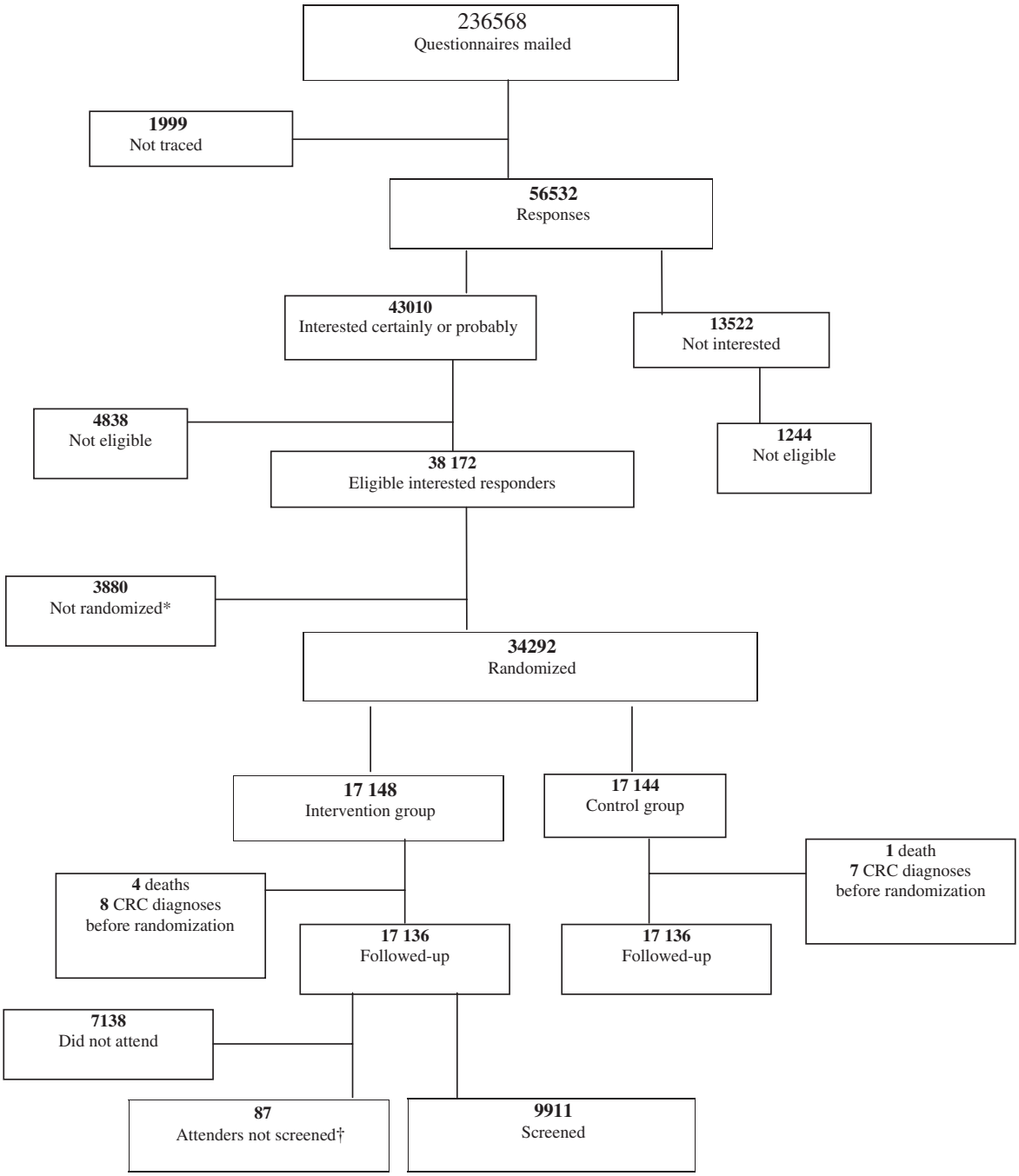

Figure 1. Flow diagram of subjects in the Screening for Colon Rectum (SCORE) trial. **Asterisk** indicates that based on the low response rate observed in Genoa among people responding that they would probably have the test if invited, these subjects where no longer randomized in that center, starting from December, 1996. **Dagger** indicates one subject who refused to repeat flexible sigmoidoscopy following inadequate bowel preparation; this subject was diagnosed with colorectal cancer before the random assignment and was excluded from the follow-up analysis. CRC = colorectal cancer.

containing a brief description of the procedure and mentioning its possible side effects was included. A reminder letter was mailed to all nonattenders. Recruitment began on June 14, 1995, and was completed by May 10, 1999.

Flexible Sigmoidoscopy Screening Procedure

Screening was undertaken by gastroenterology specialists in hospital endoscopy units. Bowel preparation was limited to a single enema, self-administered at home 2 hours before the test. No dietary restriction was recommended (16). All patients gave written consent for the screening procedure. A 140 cm colonoscope was used in all centers except Genoa, where a 60 cm sigmoidoscope was used. The aim of the examination was to advance the endoscope beyond the sigmoid-descending colon junction. No sedation was offered. If the exam could not be performed because of inadequate bowel preparation, the subject was invited to repeat the test at a later date.

Diminutive polyps (≤5 mm) were removed during flexible sigmoidoscopy using the cold snare technique (17,18). Subjects found to have larger distal polyps (>5 mm), those with inadequate bowel preparation harboring at least one polyp, and those found to have

invasive CRC cancer were referred for total colonoscopy. Total colonoscopy was also indicated, as determined by histological examination, for subjects with three or more adenomas, for subjects with one adenoma with villous component greater than 20%, or for subjects with high-grade dysplasia.

All patients detected with "high-risk" adenomas (ie, one adenoma ≥10 mm, or high-grade dysplasia, or villous component >20%), or with three or more adenomas of any type or with five or more hyperplastic polyps located proximal to the rectum were referred for total colonoscopy surveillance. Subjects with negative flexible sigmoidoscopy or with other types of polyps were discharged and offered no further follow-up.

Classification of CRC

According to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) (19), distal CRCs were those coded as 153.2 (descending colon), 153.3 (sigmoid colon), 154.0 (rectosigmoid junction), 154.1 (rectum), and 154.2 (anal canal); proximal CRCs included codes 153.0 (hepatic flexure), 153.1 (transverse colon), and 153.4–153.8 (cecum, appendix, ascending colon, splenic flexure, other specified sites of the large intestine), whereas site unspecified CRCs were those coded as 153.9.

Invasive adenocarcinomas (*ICD-O2* codes) were included in the analysis, and squamous cell carcinomas, neuroendocrine tumors, and colorectal localizations of other primary malignancies were excluded. Cancers were classified according to the World Health Organization criteria (20) as the invasion of malignant cells beyond the muscularis mucosa. Lesions with histological evidence of in situ and/or intramucosal carcinoma were classified as high-grade dysplasia adenomas. Cancer was classified as advanced if the Union for International Cancer Control (UICC) stage was III or IV (21). Staging was derived based on information contained in the medical record and reports from histology and imaging examinations. The results of a chest x-ray and of upper abdominal ultrasound and/or computed tomography performed at the time of CRC diagnosis were considered as the minimum requirement for assigning a stage in these CRCs.

Synchronous CRCs were classified based on the code of the more distal lesion. As already stated in the screening protocol (9), we also classified cancers located in the descending colon, which were often examined at screening, as distal neoplasms. We ran an analysis using the restricted definition of distal colon adopted in the other published trials, which included the rectum and sigmoid colon only, to allow for direct comparison of the results.

Follow-up of Subjects for CRC Incidence and Mortality

During the follow-up period, we performed a search every 2 years based on an automatic record linkage of the trial database with the regional hospital discharge records and the pathology department files in all geographic areas covered by our study. The record linkage was based on two independent identifiers as follows: social security number and an algorithm derived from name and birth date. For hospital discharge records, we selected *ICD-9-CM* diagnosis codes related to colorectal malignancy or codes for surgical, diagnostic, or medical procedures possibly related to CRC (Supplementary Table 1, available online). Specific software was developed for use in all centers to ensure standardization of the search procedures for the targeted *ICD-9-CM* codes.

A link was classified as positive if the social security number or the name and birthdate algorithm of a person with a discharge diagnosis of colorectal malignancy or codes of surgical or diagnostic medical procedures that were possibly related to CRC (Supplementary Table 1, available online) were matched with those of a subject recruited in the trial.

The information concerning histology, surgery, and staging, including imaging examinations, were recorded on a standard electronic form by a research assistant. Experts from the local cancer registries used this information for assessing the diagnoses of all candidate cases of CRC and then classified primary CRCs according to the standard cancer registration rules (22). Population cancer registries cover the geographic areas of five of the six participating centers (Arezzo, Biella, Genoa, Rimini, and Turin). In Milan, where the recruitment area of the trial extended beyond the city boundaries (23), experts from the city cancer registry (24), which is active since 2002, classified all CRCs identified in the recruitment area. Experts assessing CRC cases were blinded to the allocation of the subjects to the intervention or control group at randomization.

The vital status at the end of follow-up period was ascertained for all trial subjects through an automated record linkage with the regional mortality registries, which also record the causes of death. We retrieved the death certificates of all patients who had been diagnosed with CRC during the follow-up. An independent panel of experts from the population cancer registries covering the trial centers, who were blinded to random assignment of subjects to trial groups, reviewed these certificates and reassigned the underlying cause of death. Death certificates were supplemented by clinical information, when available. The follow-up for CRC incidence ended in all centers on December 31, 2007.

Mortality follow-up was completed on December 31, 2008, in five centers (Turin, Biella, Milan, Rimini, and Arezzo), whereas in the remaining center (Genoa) it was completed on December 31, 2007, because of a delay in the updating of the mortality registry at this center.

Statistical Analysis

As mentioned earlier (9), we planned to enroll 40 000 eligible respondents and to achieve an attendance rate of about 70% in the screening group. Based on the age-specific incidence rates for the period 1988–1992, as reported in the local cancer registries (24), and assuming a weighted average lead time of screen-detected CRC of 3.5 years (25), the planned sample size and attendance rate provided 80% power to detect a statistically significant (at 5% level) reduction of 21% after 6 years of follow-up (one-sided test), or 18% after 10 years of follow-up (two-sided test), in the incidence of CRC in the intervention group. Based on the same assumptions, a statistically significant reduction in mortality was expected to be detected after 11 years of follow-up.

The primary outcomes of the analysis were CRC incidence and CRC-specific mortality. Secondary outcomes were incidence of distal and proximal CRC, incidence of advanced (UICC stages III and IV) CRC, all-cause mortality, and mortality not related to CRC. Subjects who moved outside the geographic areas covered by the regional archives used for the mortality and incidence

follow-up were classified as "emigrated" in our analysis. The follow-up time of people who emigrated, were diagnosed with CRC, or died was censored at the date of the event.

We computed the average incidence rates per 100 000 person-years and the rate ratios (RRs) with 95% confidence intervals (CIs), in intention-to-treat and in per-protocol analyses. The rate ratios adjusted for noncompliance were estimated in the per-protocol analysis, using the method proposed by Cuzick et al. (26), which allows obtaining an unbiased estimate of the magnitude of the treatment effect among compliers, accounting for randomization. Rate ratios were also calculated separately for sex and age at randomization (two categories: 55–59and 60–64 years). We analyzed time to CRC and time to death by estimating the Nelson–Aalen cumulative hazard function and computed the cumulative hazard ratios (HR) for estimating the risk of cancer among screened subjects who were negative at screening. All statistical tests were two-sided and *P* values less than .05 were considered to be statistically significant.

Results

Compliance and Management of Trial Subjects

We reported earlier (9) that of the 17 148 subjects randomly assigned to the intervention group in the SCORE trial, 9999 (58.3%) subjects attended the screening and 9911 subjects were examined by flexible sigmoidoscopy. The remaining 88 subjects, who were referred for a second examination because of inadequate bowel preparation, did not return to be screened. Of the 9911 subjects screened, 9387 (94.71%) subjects were discharged, 55 (0.55%) subjects were referred for surgery (43 CRCs, 10 large adenomas, and two perforations: one during flexible sigmoidoscopy and one during total colonoscopy), 395 (4.0%) subjects were referred for a subsequent surveillance colonoscopy, whereas the remaining 74 (0.74%) subjects did not comply with the recommended total colonoscopy assessment. The detection rate for CRC was 5.4 per 1000 subjects; 54 subjects were detected with 57 CRCs (44 in the rectum and sigmoid colon, four in the descending colon, and nine in the proximal colon). Treatment was limited to endoscopic excision in 11 of the 29 subjects detected with UICC stage I CRC.

Because the study cohort database was linked with the regional archives, we could check incidence and vital status of the subjects. We found that five subjects (four in the intervention group, one in the control group) had died, and 15 subjects were diagnosed with CRC (eight in the intervention group, seven in the control group) before the date of random assignment (Figure 1). These subjects were excluded from the follow-up analysis. Of the 12 subjects excluded in the intervention group, one subject had attended screening but refused to return for a second examination because of inadequate bowel preparation. Therefore, the final analysis cohort consisted of 34 272 subjects: 17 136 subjects randomly assigned to the intervention group, who were invited for flexible sigmoidoscopy screening, and 17,136 subjects randomly assigned to the control group who were not contacted further. Of the 17 136 subjects in the intervention group, 9911 were screened (as already reported) and 7225 (7138 nonattenders and 87 attenders who were not examined) were not screened. There were 50.0% men in the intervention group and 50.5% in the control group, and the mean ages were 59.7 (95%CI = 55.5 to 64.3) years and 59.6 (95% CI = 55.5 to 64.4) years, respectively. The demographic characteristics of the randomized groups have been described previously (9).

Follow-up of CRC Incidence and Mortality in the SCORE Trial Subjects

During follow-up, 280 (1.6%) subjects in the intervention group and 324 (1.9%) subjects in the control group could not be traced. The median follow-up time to death, emigration, or end of follow-up was 10.5 years (interquartile range = 9.9–11.3) for incidence and 11.4 years (interquartile range = 10.8–11.9) for mortality.

A total of 609 study subjects were diagnosed with invasive CRCs, which included CRC detected by flexible sigmoidoscopy screening. After excluding 29 subjects with in situ CRCs (reclassified as adenomas with high-grade dysplasia), 14 subjects with squamous cell carcinomas, five subjects with carcinoid tumors, three subjects with metastatic cancers, and one subject with sarcoma, 557 subjects with invasive large bowel malignancies were included in the incidence analysis. Of the 557 subjects, 251 subjects were in the intervention group (135 subjects with CRC in rectum and sigmoid colon, 44 subjects with CRC detected at screening, 17 subjects with CRC in the descending colon, four subjects with CRC detected at screening) and 306 subjects were in the control group (176 in the rectum and sigmoid colon and 22 in the descending colon). The histology report was available for 554 subjects; two subjects with CRC were clinically diagnosed and one subject with CRC was ascertained through the death certificate only.

Of the 251 subjects with CRC in the intervention group, 126 were screened, and 54 (42.8%) of these screened subjects were identified at the flexible sigmoidoscopy screening and this proportion, among screened subjects, increased to 67.6% (48 of 71 subjects), when considering the subjects with distal colon (rectum, sigmoid, and descending colon) cancers.

Overall incidence rates in the intervention and control groups were 144.11 and 176.43, respectively, per 100 000 person-years. In the intention-to-treat analysis (Table 1), the overall incidence rate of CRC in the intervention group was reduced by 18% (RR = 0.82, 95% CI = 0.69 to 0.96) compared with the control group. The CRC incidence rate in the distal colon was reduced by 24% (RR = 0.76, 95% CI = 0.62 to 0.94), whereas the incidence rate in the proximal colon reduced by 9% (RR = 0.91, 95% CI = 0.69 to 1.20). We observed a more favorable stage distribution for subjects diagnosed with CRC in the intervention group, and incidence rate of advanced CRCs (UICC stage III or more advanced) showed a 27% reduction (RR = 0.73, 95% CI = 0.58 to 0.94). In the adjusted per-protocol analysis (Table 2), CRC incidence rate was reduced by 31% (RR = 0.69, 95% CI = 0.56 to 0.86) among screening attenders, the reduction being greater in the distal colon (RR = 0.60, 95% CI = 0.46 to 0.80) than in the proximal colon (RR = 0.85, 95% CI = 0.61 to 1.19).

These estimates did not change substantially when a stricter definition of distal lesions (ie, rectum and sigmoid colon only) was used for analysis. In the intention-to-treat and per-protocol analyses, the rate of CRC incidence in the distal colon was reduced by 24% (RR = 0.76, 95% CI = 0.61 to 0.96) and 39% (RR = 0.61, 95% CI = 0.45 to 0.81), and in the proximal colon by 11% (RR = 0.89, 95% CI = 0.69 to 1.14) and 21% (RR = 0.79, 95% CI = 0.56 to

Table 1. CRC incidence and mortality among the SCORE trial subjects by intention-to-treat analysis*

CRC incidence	Control group† 173 437 person-years§ No. of subjects with CRC	Control group† 173 437 person-years§ Rate per 100 000 person-years (95% CI)	Intervention group‡ 174 177 person-years§ No. of subjects with CRC	Intervention group‡ 174 177 person-years§ Rate per 100 000 person-years (95% CI)	Intervention vs control group RR (95% CI)
All sites	306	176.43 (157.73 to 197.35)	251	144.11 (127.34 to 163.08)	0.82 (0.69 to 0.96)
Distal‖	198	114.16 (99.32 to 131.22)	152	87.27 (74.44 to 102.30)	0.76 (0.62 to 0.94)
Proximal¶	108	62.27 (51.57 to 75.19)	99	56.84 (46.68 to 69.21)	0.91 (0.69 to 1.20)
Advanced CRC#					
All sites	152	87.64 (74.76 to 102.74)	112	64.30 (53.43 to 77.38)	0.73 (0.57 to 0.94)
Distal‖	90	51.89 (42.21 to 63.80)	69	39.61 (31.29 to 50.16)	0.76 (0.56 to 1.04)
Proximal¶	62	35.75 (27.87 to 45.85)	43	24.69 (18.31 to 33.29)	0.69 (0.47 to 1.02)

CRC mortality	Control group† 186 745 person-years** No. of deaths	Control group† 186 745 person-years** Rate per 100 000 person-years (95% CI)	Intervention group‡ 187 532 person-years** No. of deaths	Intervention group‡ 187 532 person-years** Rate per 100 000 person-years (95% CI)	Intervention vs control group RR (95% CI)
All deaths among subjects diagnosed with CRC††					
All sites	94	50.34 (41.12 to 61.61)	71	37.86 (30.00 to 47.77)	0.75 (0.55 to 1.02)
Distal‖	55	29.45 (22.61 to 38.36)	40	21.33 (15.65 to 29.08)	0.72 (0.48 to 1.09)
Proximal¶	39	20.88 (15.26 to 28.58)	31	16.53 (11.62 to 23.50)	0.79 (0.49 to 1.27)
CRC deaths					
All sites	83	44.45 (35.84 to 55.11)	65	34.66 (27.18 to 44.20)	0.78 (0.56 to 1.08)
Distal‖	48	25.70 (19.37 to 34.11)	35	18.66 (13.40 to 25.99)	0.73 (0.47 to 1.12)
Proximal¶	35	18.74 (13.46 to 26.10)	30	16.00 (11.18 to 22.88)	0.85 (0.52 to 1.39)
Non-CRC deaths‡‡	1150	615.81 (581.23 to 652.45)	1137	606.30 (572.06 to 642.58)	0.98 (0.91 to 1.07)

* CRC incidence and mortality were analyzed by all sites, distal, and proximal cancers. CI = confidence interval; CRC = colorectal cancer; RR = rate ratio; SCORE = Screening for Colon Rectum.

† Control group includes 17 136 subjects who were not invited for flexible sigmoidoscopy screening.

‡ Intervention group includes 17 136 invited for flexible sigmoidoscopy screening.

§ Person-years at December 31, 2007, or at the date of the event for subjects who were diagnosed with CRC, or emigrated, or died.

‖ Distal CRC were those coded as 153.2 (descending colon), 153.3 (sigmoid colon), 154.0 (rectosigmoid junction), 154.1 (rectum), 154.2 (anal canal).

¶ Proximal CRCs included codes 153.0 (hepatic flexure), 153.1(transverse colon), and 153.4–153.8 (cecum, appendix, ascending colon, splenic flexure, other specified sites of the large intestine).

Cancer was classified as advanced if the Union for International Cancer Control stage was III or IV (21).

** Person-years at December 31, 2008 (Turin, Biella, Milan, Rimini, Arezzo), or December 31, 2007 (Genoa), or at the date of the event for subjects who died or emigrated.

†† All deaths, related or unrelated to CRC, among subjects diagnosed with CRC.

‡‡ Non–CRC-related deaths.

1.12), respectively (data not shown). In both intention-to-treat and per-protocol analyses, the incidence reduction was numerically larger among women and subjects older than 60 years of age, although the 95% confidence intervals overlapped to a large extent in the two analyses (Table 3).

The cumulative incidence remained higher in the intervention than in the control group for about 5 years (Figure 2, A) as well as among screened subjects compared with the control group (Figure 2, B) as a result of detection of prevalent CRCs at screening in the intervention group. After that time the curves started to diverge, with a lower cumulative incidence in the intervention group compared with the control group, and the trend was still maintained after 10 years of follow-up (Figure 2, A). The cumulative incidence trend was similar among subjects in the control group and among those who were not screened (Figure 2, B). These same trends can be observed for distal and advanced CRC incidence (Figure 3, A, B, E, and F) but not yet for proximal CRC (Figure 3, C and D).

Among subjects with negative screening examination results (Table 4), the rate of CRC incidence (interval cancers) remained lower than in the control group over the entire follow-up period. Even at 10 years follow-up, the cumulative incidence rate in this group was still 59% lower than expected (Nelson–Aalen cumulative HR = 0.41, 95% CI = 0.32 to 0.54) compared with the control group. The reduction was even larger when considering only distal CRCs in the screening group (Nelson–Aalen cumulative HR = 0.21; 95% CI = 0.13 to 0.32) compared with the control group.

There were 2435 deaths in the study cohort during the follow-up period (1233 in the control and 1202 in the intervention group); the cumulative all-cause mortality at the end of the 11.4 years of follow-up was 660.26 per 100 000 person-years in the control and 640.96 per 100 000 person-years in the intervention group. CRC was assigned as the underlying cause of death in 148 subjects (65 in the intervention group and 83 in the control group); CRC mortality

Table 2. CRC incidence and mortality among the SCORE trial subjects by per-protocol analysis*

	Control†	Intervention‡				
		Not screened		Screened		Rate ratio (95% CI) adjusted‖
	173437 person-years§	72832 person-years§		101345 person-years§)		
Incidence	No. of subjects with CRC	Rates per 100000 person-years (95% CI)	No. of subjects with CRC	Rates per 100000 person-years (95% CI)	No. of subjects with CRC	Rates per 100000 person-years (95% CI)	Screened vs control group
All sites	306	176.43 (157.73 to 197.35)	125	171.63 (144.03 to 204.51)	126	124.33 (104.41 to 148.05)	0.69 (0.56 to 0.86)
Distal¶	198	114.16 (99.32 to 131.22)	81	111.21 (89.45 to 138.27)	71	70.06 (55.52 to 88.40)	0.60 (0.46 to 0.80)
Proximal#	108	62.27 (51.57 to 75.19)	44	60.41 (44.96 to 81.18)	55	54.27 (41.67 to 70.69)	0.85 (0.61 to 1.19)
Advanced CRC**							
All sites	152	87.64 (74.76 to 102.74)	64	87.87 (68.78 to 112.27)	48	47.36 (35.69 to 62.85)	0.54 (0.39 to 0.76)
Distal¶	90	51.89 (42.21 to 63.80)	46	63.16 (47.31 to 84.32)	23	22.70 (15.08 to 34.15)	0.52 (0.31 to 0.86)
Proximal#	62	35.75 (27.87 to 45.85)	18	24.71 (15.57 to 39.23)	25	24.67 (16.67 to 36.51)	0.56 (0.36 to 0.87)

	Control†	Intervention‡				
		Not screened		Screened		Rate ratio (95% CI) adjusted‖
	186745 person-years††)	(78586 person-years††)		(108946 person-years††)		
Mortality	No. of deaths	Rates per 100000 person-years (95% CI)	No. of deaths	Rates per 100000 person-years (95% CI)	No. of deaths	Rates per 100000 person-years (95% CI)	Screened vs control group
All deaths among subjects diagnosed with CRC‡‡							
All sites	94	50.34 (41.12 to 61.61)	38	48.35 (35.18 to 66.44)	33	30.29 (21.53 to 42.61)	0.58 (0.38 to 0.87)
Distal¶	55	29.45 (22.61 to 38.36)	26	33.08 (22.52 to 48.58)	14	12.85 (7.61 to 21.70)	0.50 (0.26 to 0.94)
Proximal#	39	20.88 (15.26 to 28.58)	12	15.27 (8.67 to 26.88)	19	17.44 (11.12 to 27.34)	0.66 (0.39 to 1.12)
CRC deaths							
All sites	83	44.45 (35.84 to 55.11)	35	44.54 (31.97 to 62.02)	30	27.54 (19.25 to 39.38)	0.62 (0.40 to 0.96)
Distal¶	48	25.70 (19.37 to 34.11)	23	29.27 (19.45 to 44.03)	12	11.01 (6.25 to 19.39)	0.48 (0.24 to 0.94)
Proximal#	35	18.74 (13.45 to 26.10)	12	15.27 (8.67 to 26.89)	18	16.52 (10.41 to 26.22)	0.78 (0.45 to 1.35)
Non-CRC deaths§§							
	1150	615.81 (581.23 to 652.45)	603	767.31 (708.32 to 830.91)	534	490.15 (450.29 to 533.54)	0.97 (0.85 to 1.09)

* CRC incidence and mortality were analyzed by all sites, distal, and proximal cancers. CI = confidence interval; CRC = colorectal cancer; RR = rate ratio; SCORE = Screening for Colon Rectum.

† Control group includes 17136 subjects not invited for flexible sigmoidoscopy screening.

‡ Intervention group includes 17136 invited for flexible sigmoidoscopy screening: 7225 not screened and 9911 screened subjects.

§ Person-years at December 31, 2007, or at the date of the event for subjects who were diagnosed with CRC or emigrated, or died.

‖ Cuzick et al. method (26).

¶ Distal CRC were those coded as 153.2 (descending colon), 153.3 (sigmoid colon), 154.0 (rectosigmoid junction), 154.1 (rectum), 154.2 (anal canal).

Proximal CRCs included codes 153.0 (hepatic flexure), 153.1(transverse colon), and 153.4–153.8 (cecum, appendix, ascending colon, splenic flexure, other specified sites of the large intestine).

** Cancer was classified as advanced if the Union for International Cancer Control stage was III or IV (21).

†† Person-years at December 31, 2008 (Turin, Biella, Milan, Rimini, Arezzo), or December 31, 2007 (Genoa), or at the date of the event for subjects who died or emigrated.

‡‡ All deaths related or unrelated to CRC.

§§ Non–CRC-related deaths.

Table 3. CRC incidence by sex and age at randomization by intention-to-treat and per-protocol analysis*

	Intention-to-treat analysis						
	Control group†			Intervention group‡			Intervention vs control group
	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	RR (95% CI)
Sex							
Women	118	86734	136.05 (113.36 to 162.95)	87	88 288	98.54 (79.87 to 121.58)	0.72 (0.55 to 0.96)
Men	188	86703	216.83 (187.95 to 250.15)	164	85 889	190.94 (163.85 to 222.52)	0.88 (0.71 to 1.09)
Age, y‖							
55–59	157	98773	158.95 (135.93 to 185.86)	131	97 980	133.70 (112.66 to 158.67)	0.84 (0.67 to 1.06)
>60	149	74664	199.56 (169.96 to 234.32)	120	76 197	157.49 (131.69 to 188.34)	0.79 (0.62 to 1.00)

	Per-protocol analysis									
				Intervention group‡						Screened vs control group
	Control group†			Not screened			Screened			
	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	No. of subjects with CRC	Person-years§	Rate per 100 000 person-years (95% CI)	Adjusted RR (95% CI)¶
Sex										
Women	118	86734	136.05 (113.36 to 162.95)	47	40335	116.52 (87.55 to 155.09)	40	47953	83.42 (61.19 to 113.72)	0.55 (0.39 to 0.77)
Men	188	86703	216.83 (187.95 to 250.15)	78	32497	240.02 (192.25 to 299.66)	86	53392	161.07 (130.39 to 198.98)	0.79 (0.60 to 1.06)
Age, y‖										
55–59	157	98773	158.95 (135.93 to 185.86)	65	39762	163.47 (128.19 to 208.46)	66	58218	113.37 (89.06 to 144.30)	0.73 (0.54 to 0.99)
>60	149	74664	199.56 (169.96 to 234.32)	60	33071	181.43 (140.87 to 233.67)	60	43126	139.13 (108.02 to 179.18)	0.65 (0.48 to 0.89)

* CRC incidence by all sites. CI = confidence interval; CRC = colorectal cancer; RR = rate ratio.

† Control group includes 17 136 subjects not invited for flexible sigmoidoscopy screening.

‡ Intervention group includes 17 136 subjects invited for flexible sigmoidoscopy screening: 7225 subjects were not screened and 9911 subjects were screened.

§ Person-years at December 31, 2007, or at the date of the event for subjects who were diagnosed with CRC or emigrated or died.

‖ Age at randomization.

¶ Rate ratios were adjusted for noncompliance using the method proposed by Cuzick et al. (26).

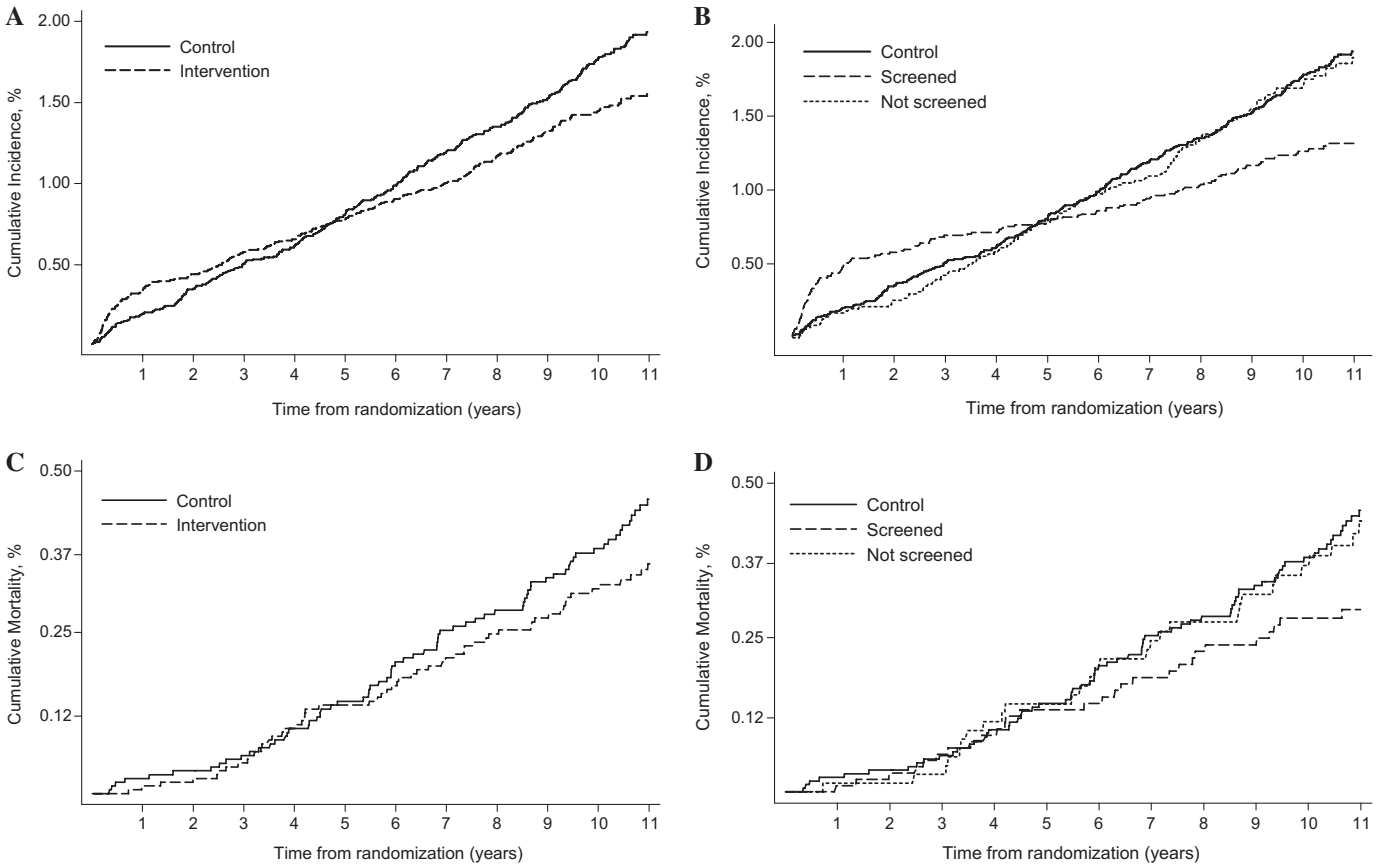

Figure 2. Nelson–Aalen cumulative incidence of colorectal cancer (CRC) and mortality by time from randomization. **A**) In the intention-to-treat analysis, cumulative incidence of CRC at all sites is shown for the control and intervention groups. **B**) In the per-protocol analysis, cumulative incidence of CRC at all sites is shown for the control, screened, and not screened groups. **C**) In the intention-to-treat analysis, cumulative mortality of CRC at all sites is shown for the control and intervention groups. **D**) In the per-protocol analysis, cumulative mortality of CRC at all sites is shown for the control, screened, and not screened groups. The cumulative incidence and mortality were estimated with the Nelson–Aalen cumulative hazard function.

rates in the intervention and control groups were 34.66 and 44.45, respectively, per 100 000 person-years.

In the intervention group as a whole, total CRC mortality was reduced by 22% (RR = 0.78, 95% CI = 0.56 to 1.08) and distal CRC mortality was reduced by 27% (RR = 0.73, 95% CI = 0.47 to 1.12) compared with the control group (Table 1). All-cause mortality (combining CRC and non-CRC-related deaths) tended to be lower among subjects diagnosed with CRC in the intervention group (RR = 0.75, 95% CI = 0.55 to 1.02) compared with CRCs in the control group (Table 1, and Figure 2, C). After adjusting for noncompliance (26) in the per-protocol analysis, total mortality and mortality from distal CRC among the screened subjects were reduced by 38% (RR = 0.62, 95% CI = 0.40 to 0.96) and 52% (RR = 0.48, 95% CI = 0.24 to 0.94), respectively, compared with the control group (Table 2, and Figure 2, D).

Discussion

This follow-up study confirmed in the SCORE trial participants that a single sigmoidoscopy screening between the ages 55 and 64 years can confer a substantial and long-lasting protective effect. Overall, in the per-protocol analysis, CRC incidence was reduced by 31% among those who underwent screening and by 40% when considering incidence in the distal colon only (rectum, sigmoid, and descending colon). The incidence reduction was larger for advanced CRC cases, which was reduced by 46% among screened subjects compared with the control group. In per-protocol analysis, 10 years after the screening examination, the cumulative incidence of CRC following a negative flexible sigmoidoscopy remained 59% lower than in the control group. The observed effects of screening on CRC incidence were statistically significant also in the intention-to-treat analysis. In per-protocol analysis, CRC mortality was statistically significantly reduced by 38% among screened subjects compared with the control group, although a statistically significant reduction in CRC mortality was not yet observed in the intention-to-treat analysis.

Non–CRC-related mortality in the intervention group showed a slight (2%) although not statistically significant reduction in the intention-to-treat analysis, whereas mortality was statistically significantly reduced among screen subjects diagnosed with CRC compared with CRC subjects in the control group, in the per-protocol analysis. These findings indicate that flexible sigmoidoscopy screening is not associated with serious side effects.

Our findings are consistent with the observed reduction of total CRC incidence by 33% and distal CRC incidence by 50% among people screened in the UK Flexible Sigmoidoscopy Screening Trial

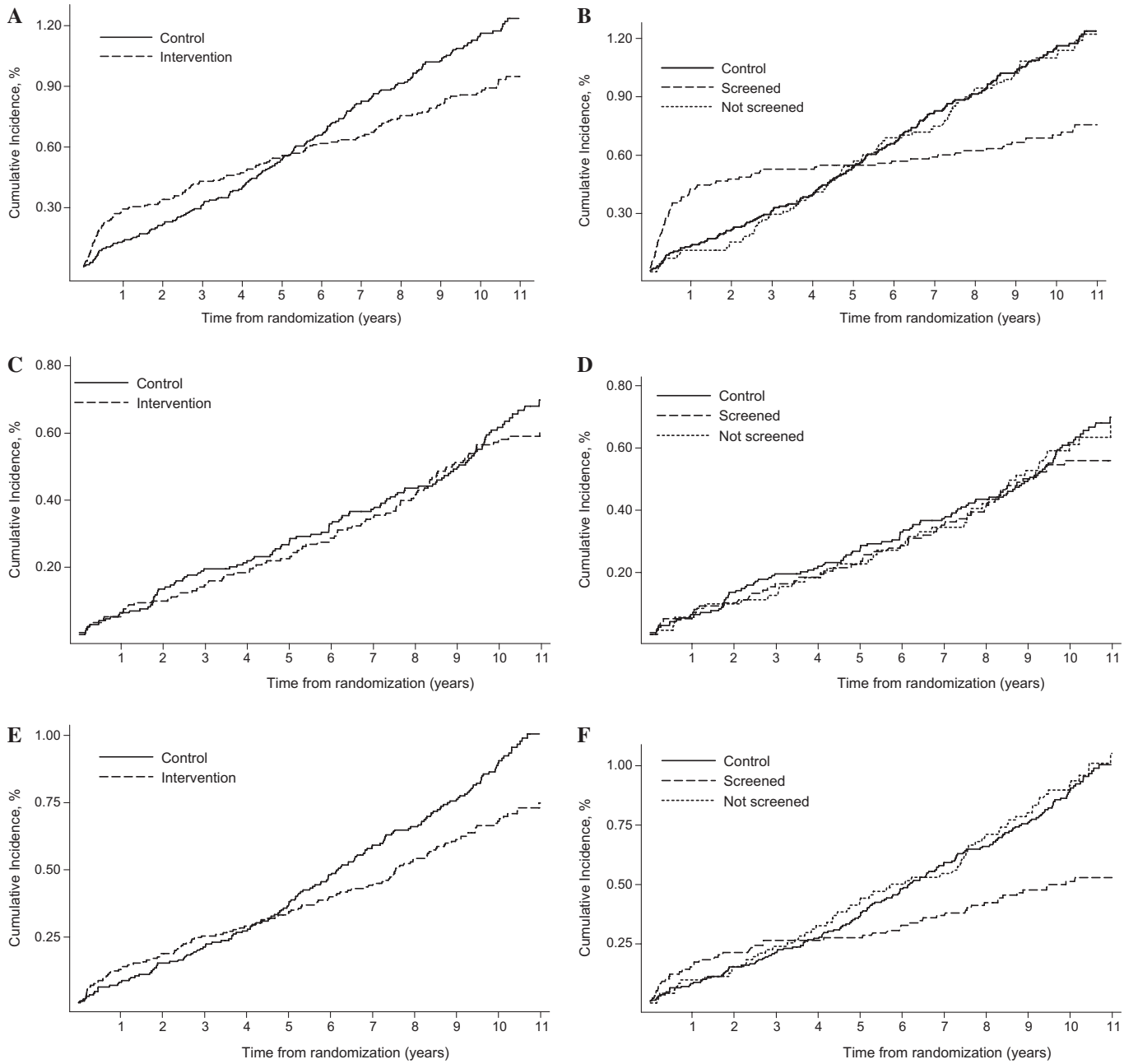

Figure 3. Nelson–Aalen cumulative incidence of colorectal cancer (CRC) by time from randomization. **A**) In the intention-to-treat analysis, cumulative incidence of distal CRC is shown for the control and intervention groups. **B**) In the per-protocol analysis, cumulative incidence of distal CRC is shown for the control, screened, and not screened groups. **C**) In the intention-to-treat analysis, cumulative incidence of proximal CRC is shown for the control and intervention groups. **D**) In the per-protocol analysis, cumulative incidence of proximal CRC is shown for the control, screened, and not screened groups. **E**) In the intention-to-treat analysis, cumulative incidence of advanced CRC is shown for the control and intervention groups. **F**) In the per-protocol analysis, cumulative incidence of advanced CRC is shown for the control, screened, and not screened groups. The cumulative incidence was estimated with the Nelson–Aalen cumulative hazard function.

(13). The lower participation rate (58% vs 71%) and the shorter duration of the incidence follow-up (10.5 vs 11.2 years) largely explain the observed differences in the estimates of screening effect in the intention-to-treat analysis, with a lower reduction of overall (18% vs 23%) and distal (24% vs 36%) CRC incidence in the SCORE trial vs the UK trial (13). Similar to the UK trial, the difference in the cumulative incidence between intervention and control groups in the SCORE trial shows a trend toward an increase with time, which is still apparent at the end of the 10.5 years follow-up period. This suggests that the overall effect of screening is not yet fully observed after 10 years.

As in other published trials (13,14), CRC incidence in our study is much higher in the intervention group in the initial period of follow-up because of detection of a high number of prevalent CRCs at screening. The higher detection rate (0.54%) at screening in our trial compared with the UK trial (0.35%) may explain, in part, why the incidence reduction started to become apparent slightly later in the SCORE trial, where the cumulative incidence curves of the intervention and control groups crossed approximately 12 months later. The observed reduction of CRC mortality among screened subjects was just

Table 4. Nelson–Aalen cumulative hazard ratios for interval cancers in screened subjects after randomization*

Years from randomization†	Interval cancers at all sites		Interval cancers at distal colon‡	
	Screened vs control	Not screened vs control	Screened vs control	Not screened vs control
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95% CI)
All subjects§				
2	0.26 (0.13 to 0.52)	0.71 (0.42 to 1.21)	0.14 (0.04 to 0.44)	0.68 (0.35 to 1.34)
4	0.31 (0.19 to 0.50)	0.94 (0.65 to 1.34)	0.13 (0.05 to 0.31)	1.00 (0.64 to 1.55)
6	0.32 (0.22 to 0.47)	0.98 (0.74 to 1.30)	0.12 (0.06 to 0.25)	1.05 (0.75 to 1.47)
8	0.39 (0.28 to 0.52)	1.01 (0.79 to 1.28)	0.16 (0.10 to 0.28)	1.03 (0.77 to 1.38)
10	0.41 (0.32 to 0.54)	0.97 (0.78 to 1.20)	0.21(0.13 to 0.32)	0.96 (0.73 to 1.25)
Men‖				
2	0.26 (0.11 to 0.62)	0.60 (0.28 to 1.28)	0.15 (0.04 to 0.65)	0.69 (0.28 to 1.71)
4	0.32 (0.17 to 0.58)	1.21 (0.77 to 1.88)	0.17 (0.06 to 0.47)	1.44 (0.86 to 2.41)
6	0.30 (0.18 to 0.49)	1.11 (0.78 to 1.59)	0.16 (0.08 to 0.36)	1.27 (0.85 to 1.91)
8	0.41 (0.28 to 0.59)	1.21 (0.90 to 1.63)	0.21 (0.11 to 0.38)	1.28 (0.91 to 1.82)
10	0.39 (0.28 to 0.55)	1.06 (0.81 to 1.40)	0.21(0.12 to 0.35)	1.21 (0.88 to 1.67)
Women¶				
2	0.24 (0.07 to 0.80)	0.90 (0.43 to 1.87)	0.11 (0.01 to 0.84)	0.72 (0.26 to 1.99)
4	0.30 (0.13 to 0.67)	0.66 (0.35 to 1.23)	0.06 (0.01 to 0.48)	0.48 (0.20 to 1.17)
6	0.35 (0.19 to 0.64)	0.87 (0.55 to 1.38)	0.04 (0.01 to 0.31)	0.79 (0.43 to 1.45)
8	0.33 (0.19 to 0.56)	0.82 (0.55 to 1.22)	0.06 (0.01 to 0.24)	0.75 (0.44 to 1.26)
10	0.44 (0.29 to 0.67)	0.90 (0.64 to 1.26)	0.20 (0.09 to 0.44)	0.65 (0.40 to 1.07)

* Interval cancers were analyzed for all sites and distal colorectal cancers. CI = confidence interval; HR = Nelson–Aalen cumulative hazard ratio.

† Years of follow-up from randomization for all subjects, men, and women.

‡ Distal colorectal cancers were those coded as 153.2 (descending colon), 153.3 (sigmoid colon), 154.0 (rectosigmoid junction), 154.1 (rectum), 154.2 (anal canal).

§ 34272 subjects (17136 subjects in the control group; 7225 not screened and 9911 screened subjects).

‖ 17221 men (8654 men in the control group; 3298 not screened and 5269 screened men).

¶ 17051 women (8482 women in the control group; 3927 not screened and 4642 screened women).

slightly lower in the SCORE trial (38%) than in the UK trial (43%) (13).

The protocol adopted in our study was similar to the protocol (27) adopted in the UK trial. The main difference in the two trials was the criteria for colonoscopy referral. Whereas in the UK trial, only subjects with large distal polyps (≥10 mm) or with smaller advanced adenomas (<10 mm) were referred for total colonoscopy, in the SCORE trial, total colonoscopy referral was indicated for subjects with small advanced adenomas (≤5 mm) and for all subjects with any distal polyp larger than 5 mm to increase the sensitivity of screening for advanced proximal neoplasia. If the same criteria for high-risk distal lesions had been adopted in Italy as in the United Kingdom, only 4.9% of people screened would have been referred for colonoscopy, instead of 8.4%. It is possible that the higher colonoscopy rate was responsible for the larger reduction of proximal CRC incidence in the SCORE trial (15%) compared with the UK trial (3%). However, consistent with other studies (28–30), an analysis conducted in the context of our trial showed that the prevalence of advanced proximal lesions was 1.9% among people harboring only 6–9 mm distal polyps as compared with 9.9% among patients with high-risk distal polyps according to the criteria adopted in the UK trial (31). Therefore, lower referral threshold is not efficient in identifying subjects at high risk for proximal neoplasia.

The participation rate for total colonoscopy assessment was 93% in the SCORE trial (775 of the 832 subjects referred to total colonoscopy), and the average completion rate of total colonoscopy was 76% (587 of 775 subjects). A complete examination of the colon could be achieved in 87% of people undergoing total colonoscopy, because of the 188 subjects with incomplete colonoscopy, 76 subjects underwent a double-contrast barium enema and 14 subjects had a complete examination when they repeated the colonoscopy. No additional neoplasia was detected in these subjects. However, we cannot exclude the fact that advanced adenomas may have been missed in the proximal colonic segments, thus reducing the potential for a preventive effect.

In the SCORE trial, we used a broader definition of distal colon than in the other published trials (13,14) by including the descending colon together with the rectum and sigmoid. Indeed, about 8% of all advanced neoplasms (including 4 of 48 CRCs) detected by the flexible sigmoidoscopy screening were located in the descending colon, probably as a result of the use of 140 cm flexible scope in five of the six centers. Because we observed a similar reduction of CRC incidence in the descending colon as in the rectum and sigmoid, the screening effect on proximal incidence would be amplified when including the descending among the proximal colonic segments.

One of the limitations of our trial is related to the self-selection of recruited subjects as a result of low proportion of questionnaire responders (23.9%), because volunteers may show a different risk profile compared with the source population. Indeed, a 46% lower CRC mortality rate was observed among the control subjects compared with the source population (data not shown). This lower mortality rate in the control subjects reduced the power of our study. Given the self-selection of the recruited subjects, a statistically significant difference in mortality of 25% between the control and intervention groups will not be detectable before 14 years of follow-up. The self-selection was confirmed by comparing the source population in Turin and Genoa with subjects recruited in the trial. The proportion of people with high school or university degree was 50%

higher among subjects enrolled in these two centers (20 228 subjects) than in the target population sample (154 374 subjects who were mailed the interest-in-screening questionnaire), with a parallel 35% decrease in the proportion of those with primary school degree only (data not shown). Previous studies (32) already showed that CRC mortality is lower among the better educated, likely as a result of a reduced diagnostic delay and of a more favorable stage distribution of CRCs. Another limitation of the trial is related to the two-stage recruitment procedure aiming to increase the power of the study in assessing screening efficacy. The self-selection process associated with the low response rate to the interest-in-screening questionnaire would reduce the generalizability of results. Nevertheless, it was not as important with respect to CRC risk as it was for mortality. The cumulative CRC incidence in the control group was approximately the same as expected (306 CRCs observed vs 316 CRCs expected), based on age-, sex-, and calendar period–specific incidence rates. This would suggest that the observed effect of screening on CRC incidence might be generalizable to the source population. An additional limitation of the study is the implementation of population-based screening programs for CRC using immunochemical FOBT (33) in the areas covered by five of the six study centers between 2004 and 2006, whereas no program was ongoing in Genoa as of December 31, 2008. The implementation of the FOBT screening programs was generally gradual, and people recruited in this trial were invited in the late roll-out period, not earlier than 2006. We could link the study database with the regional screening database in four of those five centers: 12 (nine UICC stage I or II) of the 331 CRCs diagnosed among people recruited in the trial in these four centers were detected at screening (four CRCs in the intervention group and eight CRCs in the control group). Excluding these CRCs from the analysis, assuming that they may not have been diagnosed in the absence of screening did not change our results. Assuming a similar coverage in the remaining center as in the other four, we could expect that three to four of the 98 CRCs diagnosed in that center may have been detected at screening. In our analysis, we used the underlying causes of deaths assigned by the regional mortality registers covering the study areas. According to the results of the independent verification of the death certificates of people diagnosed with an incident CRC during the follow-up, one further death was attributed to CRC, whereas two other deaths should not have been attributed to CRC. These findings suggest that the classification of the CRC deaths was accurate and consistent across the different mortality registers. As a consequence, the results would not be changed when using the causes reclassified by the independent panel in the mortality analysis.

According to a previous report (34), up to 65% of advanced neoplasms would be missed among women who showed a higher proportion of advanced proximal lesions compared with men, if they were screened with flexible sigmoidoscopy alone. Our findings do not support such hypothesis showing that the protective effect of a single flexible sigmoidoscopy screening is similar in men and women, at least in the age range of 55–64 years. We did not observe any difference in the protective effect of screening according to age when considering two age groups (55–59 and 60–64 years). Pooled analyses of the UK and SCORE trials may be necessary to assess the hypothesis suggesting that the optimal age for screening may be at around the age of 60 years (8).

Existing screening guidelines (35) recommend a 5-year interval for flexible sigmoidoscopy. The long-lasting reduction of the CRC risk among people with a negative flexible sigmoidoscopy, consistent with results of previous observational studies (4), would indicate that no substantial increase in the protective effect of screening can be expected by repeating flexible sigmoidoscopy before 10 years. In fact, the substantial risk reduction lasting over 12 years observed in the UK trial together with the observed trend toward an increase of the difference in the cumulative incidence between intervention and control group would suggest that flexible sigmoidoscopy screening may not need to be repeated.

In conclusion, our results confirm that flexible sigmoidoscopy screening offered just once represents a safe and effective method for CRC screening and ensures a long-lasting reduction of CRC risk. A longer follow-up is needed to fully assess the impact on mortality and to estimate the duration of the protective effect.

APPENDIX

The six contributing centers and members of the SCORE Working Group are the following:

Arezzo: A. Carnevali, Pathology Unit, San Donato Hospital, Azienda Unità Sanitaria Locale 8 Arezzo; A. Agnolucci and P. Ceccatelli, Endoscopy Unit, San Donato Hospital, Azienda Unità Sanitaria Locale 8 Arezzo; F. Mirri, Screening Unit, Valdarno Hospital.

Biella: A. Azzoni, Gastroenterology Unit, Infermi Hospital, Azienda Sanitaria Locale Biella; M. Giudici, Pathology Unit, Infermi Hospital, Azienda Sanitaria Locale Biella; G. Genta and A. Marutti, Edo Tempia Foundation.

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Milan: C. Zocchetti, Regional Health Authority, Regione Lombardia; M. Autelitano, Epidemiology Unit, Azienda Sanitaria Locale Città di Milano; G. Fiori, Endoscopy Unit, European Institutre of Oncology.

Rimini: G. Fabbretti, Pathology Unit, Infermi Hospital, Azienda Unità Sanitaria Locale Rimini; S. Gasperoni, Gastroenterology Unit, Santa Maria delle Croci Hospital, Ravenna.

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Funding

This work was supported by a grant from the Associazione Italiana per la Ricerca sul Cancro from 1995 to 1997 (1182/95 to Azienda Sanitaria Locale 1-Torino; N.S.) and a grant from the Italian National Research Council (CNR) (95.00539. PF39 and 96.00736.PF39 allocated to Azienda Sanitaria Locale 1-Torino; N.S.). The Istituto Oncologico Romagnolo (IOR), the Fondo "E Tempia," the University of Milano, and the Local Heath Unit Azienda Sanitaria Locale 1-Torino supported the implementation of the study in Rimini, Biella, Milano, and Torino, respectively, through own contribution within screening centers.

Notes

The authors are solely responsible for the study design, data collection, analysis and interpretation of the data, writing the article, and decision to submit the article for publication.

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