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Effects of Attendance to an Organized Fecal Immunochemical Test Screening Program on the Risk of Colorectal Cancer: An Observational Cohort Study

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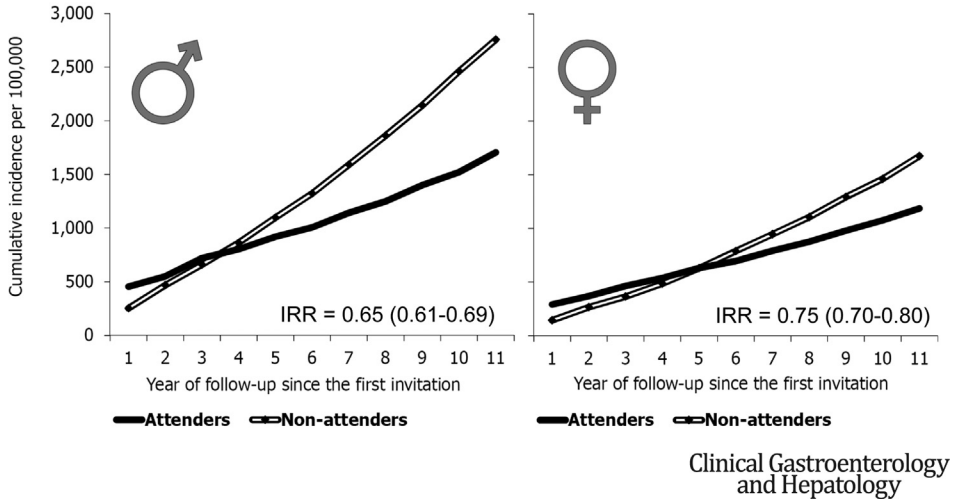
Curve of cumulative age-standardized colorectal cancer incidence rates among attenders and non-attenders to the Emilia-Romagna Region (northern Italy) biennial fecal immunochemical test screening program and incidence rate ratio with 95% confidence interval, by sex



BACKGROUND & AIMS: **This cohort study compared colorectal cancer (CRC) incidence and mortality between people who participated in an Italian regional biennial fecal immunochemical test (FIT) screening program and people who did not.**

[a]Omero Triossi died on June 6, 2021. This study is dedicated to his memory.

Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; gFOBT, guaiac-based fecal occult blood test; FIT, fecal immunochemical test; IRR, incidence rate ratio; MRR, mortality rate ratio.

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METHODS: **The program started in 2005. The target population included over 1,000,000 people aged 50 to 69 years. The FIT was a one-sample OC-Sensor (Eiken Chemical Co, Tokyo, Japan) (cutoff, ≥20 μg hemoglobin/g feces). The average annual response rate to invitation was 51.4%. The records of people invited up to June 2016 were extracted from the screening data warehouse. Attenders were subjects who responded to the first 2 invitations or to the single invitation sent them before they became ineligible. Non-attenders were subjects who did not respond to any of these invitations. The records were linked with the regional CRC registry. People registered up to December 2016 were identified. Self-selection-adjusted incidence rate ratios (IRRs) and incidence-based CRC mortality rate ratios (MRRs) for attenders to non-attenders, with 95% confidence intervals (CIs), were calculated.**

RESULTS: **The cohort generated 2,622,131 man-years and 2,887,845 woman-years at risk with 4490 and 3309 CRC cases, respectively. The cohort of attenders was associated with an IRR of 0.65 (95% CI, 0.61–0.69) for men, 0.75 (95% CI, 0.70–0.80) for women and 0.69 (95% CI, 0.66–0.72) for both sexes combined. The self-selection-adjusted IRR was 0.67 (95% CI, 0.62–0.72) for men and 0.79 (95% CI, 0.72–0.88) for women. The IRR for stage I, II, III, and IV CRC was 1.35 (95% CI, 1.20–1.50), 0.61 (95% CI, 0.53–0.69), 0.60 (95% CI, 0.53–0.68) and 0.28 (95% CI, 0.24–0.32) for men and 1.64 (95% CI, 1.43–1.89), 0.60 (95% CI, 0.52–0.69), 0.73 (95% CI, 0.63–0.85) and 0.35 (95% CI, 0.30–0.42) for women. The overall incidence-based CRC MRR was 0.32 (95% CI, 0.28–0.37) for men, 0.40 (95% CI, 0.34–0.47) for women and 0.35 (95% CI, 0.31–0.39) for both sexes combined. The adjusted MRR was 0.35 (95% CI, 0.29–0.41) for men and 0.46 (95% CI, 0.37–0.58) for women.**

CONCLUSIONS: **Attendance to a FIT screening program is associated with a CRC incidence reduction of 33% among men and 21% among women, and a CRC mortality reduction of 65% and 54%, respectively.**

Keywords: Cohort Study; Colorectal Cancer; Fecal Immunochemical Test; Incidence; Mass Screening.

See editorial on page 2216.

Several tests are available to screen average-risk people for colorectal cancer (CRC). Colonoscopy and flexible sigmoidoscopy, followed by polypectomy if indicated, reduce CRC incidence and mortality.[1-3] Biennial screening using guaiac-based fecal occult blood tests (gFOBTs), with colonoscopic evaluation of positive results, reduces CRC mortality by 9% to 22%.[4] In the Minnesota trial, gFOBT screening was also associated with a decrease in CRC incidence,[5] which was not observed in other trials.

Currently, major expert panels recommend fecal immunochemical tests (FITs) over gFOBTs.[6,7] FITs are more sensitive for detecting advanced adenomas and CRC and have a comparable or higher level of specificity because, unlike gFOBTs, are not affected by diet. FITs are expected to have a greater impact on CRC incidence and mortality.[8] At present, however, evidence for the effectiveness of FIT screening vs no screening in reducing incidence is limited. Although simulation modeling studies provided positive results,[9,10] randomized trials are lacking.[4] With respect to observational data, a decrease in incidence was observed only in 2 small Italian studies.[11,12] A large –and positive– cohort study from the United States included people screened with FIT and colonoscopy in almost equal proportions.[13] In the One Million Taiwanese Screening Program,[14,15] the effect on total CRC incidence has not been evaluated yet.

Since 2005, people aged 50 to 69 years who live in the Emilia-Romagna Region (northern Italy) have been regularly invited to an organized FIT screening program. This article reports a cohort study of the effects of attendance. The primary objective was to compare overall and sex-, age-, tumor stage- and tumor site-specific CRC incidence rates between attenders and non-attenders. The secondary objectives were to compare (1) overall and sex-, age-, tumor stage- and tumor site-specific incidence-based CRC mortality rates, and (2) overall all-cause, non-CRC-related mortality rates.

Methods

Setting

The program is delivered by 11 health care district screening units. Every 2 years, eligible people are sent a personal letter inviting them to perform a 1-sample FIT without dietary restrictions (OC-Sensor, Eiken Chemical Co, Tokyo, Japan). The cutoff for test positivity is ≥20 μg hemoglobin/g feces.

Negative FIT results are communicated by mail. Subjects testing positive are offered a complete colonoscopy under sedation or, in the case of an incomplete colonoscopy, a computed tomographic colonography. Subjects refusing assessment examinations are re-invited to FIT screening at a 2-year interval.

The classification of results of assessment examinations, the management of detected lesions, and the recommendations for colonoscopic surveillance after adenoma removal are based on the European guidelines for quality assurance in CRC screening and diagnosis.[16] Subjects with negative assessment examinations are re-invited to FIT screening at a 5-year interval.

Supplementary Table 1 shows the sex- and test-specific average annual performance measures in 3 quadrennial time periods. The estimated 12-month prevalence of people with opportunistic screening FIT and/or colonoscopy in the target population was 1.4%. Further information can be found in previously published articles.[17]

Sources of Data

The regional CRC screening data warehouse was used as the basic source of data for the study.[17] The cohort was followed-up for invasive CRC incidence through record linkage with the population-based regional CRC registry.

The study was restricted to 6 health care districts where record linkage could be done in accordance with personal data privacy regulations. On January 1, 2005, the target population living in these areas comprised 255,496 men and 270,875 women.

Eligibility Criteria

Eligible for inclusion were all people who (1) were living in the above 6 health care districts, (2) had not had a diagnosis of CRC before the date of their first invitation to screening, (3) were invited for their first FIT between 2005 and June 30, 2016, (4) were aged 50 to 69 years at the first invitation, (5) received 2 invitations or, alternatively, received 1 invitation and then became ineligible for the second, and (6) had at least 1 day of follow-up.

The reasons for ineligibility for re-invitation included positive FIT result with colonoscopy assessment, reaching of the age of 70 years, migration outside the regional borders, registration of a CRC, death, and end of follow-up (December 31, 2016)

Definition of Attendance and Non-attendance to Screening

Attenders were subjects who responded to the first 2 invitations or to the single invitation sent them before they became ineligible. Non-attenders were subjects who did not respond to any of these invitations.

Those subjects who responded to 1 invitation of 2 (non-compliant attenders) were excluded because their definition was inherently associated with a biased temporal distribution of CRC incidence, as is explained in Supplementary Figure 1.

What You Need to Know

Background

Observational studies on the effectiveness of fecal immunochemical test (FIT) as a colorectal cancer (CRC) screening tool have consistently reported an effect on mortality while providing unclear evidence for a decrease in incidence.

Findings

At 11 years of follow-up, this large cohort study from Italy associated attendance to FIT screening with a self-selection-adjusted decrease of 33% (men) and 21% (women) in CRC incidence. The effect emerged sooner and was more pronounced with increasing tumor stage, and was coupled with a reduction of 65% (men) and 54% (women) in incidence-based CRC mortality.

Implications for patient care

These results might encourage the adoption of FIT as a routine CRC screening tool as well as the implementation of organized FIT screening programs.

Follow-up

Person-years at risk and years of follow-up were counted from the date of the first invitation to the date of registration of CRC or the date of censoring (ie, migration outside the regional borders, death, or end of follow-up). The follow-up period was coincident with the accrual period. According to a validated approach,[18] follow-up was truncated at 11 years (the 75th percentile of available follow-up times).

Composition of the Cohort

The original data set comprised 468,042 men and 495,543 women invited at least once. Of these, 342,281 men and 365,470 women were eligible. The median follow-up time was 9.5 years. Supplementary Table 2 and Supplementary Table 3 show the characteristics of the cohort.

Validation of the Definition of Attendance and Non-attendance

Of the 380,651 subjects who did respond to both of the first 2 invitations, 243,081 were re-invited from once to 5 times, and 12,257 (5.0%) did never attend for screening. Specifically, of subjects invited once (n = 68,594), twice (n = 65,134), 3 times (n = 70,377), and 4 times (n = 38,903), 12.3%, 3.3%, 1.7% and 1.3%, respectively, refused all invitations (the 73 subjects invited 5 times are omitted here).

Of the 327,100 subjects who did not respond to the first 2 invitations, 207,303 were re-invited from once to 5 times, and 16,215 (7.8%) of them responded always. Specifically, of subjects invited once (n = 56,402), twice (n = 51,104), 3 times (n = 61,471), and 4 times (n = 38,105), 13.2%, 7.4%, 5.0% and 5.1%, respectively, did always accept the invitation (the 221 subjects invited 5 times are omitted here).

Statistical Methods

Subject age was calculated at the date of the first invitation. Cumulative age-standardized (2013 European standard population) CRC incidence rates were calculated. Comparison of incidence between attenders and non-attenders was based on the incidence rate ratio (IRR) with 95% confidence interval (95% CI). The IRRs were estimated with multivariable Poisson regression analysis controlling for 5-year age group.

The potential self-selection bias was adjusted for with an approach derived from Puliti et al.[18] The pre-screening CRC incidence rates were used to calculate the observed:expected ratio for CRCs among non-attenders. The expected number was obtained by multiplying the 8-year pre-screening sex- and 5-year age group-specific CRC incidence rates by the appropriate number of person-years in the cohort of non-attenders, with the sum of expected cancers being obtained with age-standardization. The self-selection-adjusted IRRs were calculated by multiplying the unadjusted IRRs by the observed:expected ratio among non-attenders. The 95% CIs were calculated using a bootstrap procedure. As a prerequisite for proper use of this method, the incidence rates in the population aged 50 to 69 years before the implementation of the program followed a stable trend (Supplementary Figure 2).

Cumulative age-standardized CRC mortality rates were calculated. Because all people in the cohort had not had a diagnosis of CRC before the date of their first invitation, mortality rates were equivalent to incidence-based mortality rates.

All-cause, non-CRC-related mortality was calculated according to the following criteria: (1) deaths from CRC were excluded by censoring follow-up at the date of CRC diagnosis; (2) subjects with CRC, diagnosed on any date, who died from causes other than CRC were included; and (3) deaths from chronic diseases other than CRC were included irrespective of the date of diagnosis. For sensitivity analysis purposes, we repeated the estimates after excluding those subjects who died within 90 days since the date of the first invitation – a characteristic supposedly associated with the likelihood of refusal.

Comparisons for CRC mortality and all-cause mortality were performed using the mortality rate ratio (MRR) with 95% CI. The MRRs were estimated with multivariable Poisson regression analysis controlling for 5-year age group.

CRC MRRs were self-selection-adjusted based on the same approach as the one used for IRRs.

The study was approved by the Ethics Committee at the Romagna Cancer Institute (ID: IRST100.37).

Results

Characteristics of Incident CRCs

The cohort generated 2,622,131 man-years and 2,887,845 woman-years at risk. In total, 4490 men and 3309 women were diagnosed with CRC. Table 1 shows their characteristics by pattern of attendance. For both sexes, the proportion of stage I patients was approximately 2-fold greater among attenders, and the opposite occurred for stage IV patients.

Annual and Cumulative CRC Incidence Rates

For attenders of both sexes, the annual CRC incidence rate peaked in year 1 since the first invitation (Supplementary Figure 1). Subsequently, the rate fell and remained below the one observed among non-attenders.

Figure 1 shows that the cumulative rates by year of follow-up since the first invitation were higher among attenders for the first 4 to 5 years. Subsequently, the curves crossed each other and diverged, so that the rate began to be higher, and increasingly so with time, among non-attenders.

Figure 2 shows the cumulative rates by year of follow-up and tumor stage among men. The underlying annual incidence rates are shown in Supplementary Table 4, and their curves in Supplementary Figure 3A. The curves of cumulative rates of stage I CRC were nearly parallel, indicating that the incidence increase occurring in year 1 for attenders was a transient one. The cumulative rate of stage II CRC was higher for attenders in the years 1 and 2. In year 3, the curves crossed each other and diverged. For stage III CRC, the temporal pattern was similar but the curves crossed in year 2. With respect to stage IV, attenders began to have a lower incidence in the very first year of follow-up.

The homologous data for women are shown in Figure 3 (cumulative rates), Supplementary Table 4 (underlying annual rates) and Supplementary Figure 3B (curves of underlying annual rates). The rates were lower than among men but the temporal pattern of cumulative incidence was very similar.

CRC Incidence Rates and Rate Ratios

Table 2 shows the formal comparison of CRC incidence rates. Among men, the overall incidence of CRC was 35% lower for attenders. These had a 35% excess incidence of stage I CRC and significant decreases for the 3 higher stage categories, with the difference being more

Table 1. Total Number, Subject Age Distribution, Tumor Stage Distribution, and Tumor Site Distribution of CRC Cases Registered Since the First Invitation to the Emilia-Romagna Region (Northern Italy) Colorectal Cancer Biennial FIT Screening Program (Year of Start, 2005), by Sex and Pattern of Response

	CRC cases among attenders (n = 3675), n (%)	CRC cases among non-attenders (n = 4124), n (%)
Sex		
Men	1994 (54.3)	2496 (60.5)
Women	1681 (45.7)	1628 (39.5)
Men		
Age, *y*		
50–54	354 (17.8)	527 (21.1)
55–59	392 (19.7)	479 (19.2)
60–64	512 (25.7)	625 (25.0)
65–69	736 (36.9)	865 (34.7)
Tumor stage[a]		
I	830 (42.3)	508 (20.7)
II	426 (21.7)	560 (22.8)
III	402 (20.5)	551 (22.4)
IV	224 (11.4)	661 (26.9)
Missing	80 (4.1)	175 (7.1)
Tumor site		
Proximal colon	723 (36.3)	750 (30.0)
Distal colon	697 (35.0)	915 (36.7)
Rectum	528 (26.5)	764 (30.6)
Anus	32 (1.6)	41 (1.6)
Site unknown[b]	14 (0.7)	26 (1.0)
Women		
Age, *y*		
50–54	373 (22.2)	405 (24.9)
55–59	361 (21.5)	331 (20.3)
60–64	390 (23.2)	337 (20.7)
65–69	557 (33.1)	555 (34.1)
Tumor stage[a]		
I	657 (40.6)	290 (18.7)
II	335 (20.7)	409 (26.4)
III	361 (22.3)	358 (23.1)
IV	195 (12.0)	400 (25.8)
Missing	71 (4.4)	93 (6.0)
Tumor site		
Proximal colon	688 (40.9)	567 (34.8)
Distal colon	575 (34.2)	549 (33.7)
Rectum	343 (20.4)	417 (25.6)
Anus	62 (3.7)	78 (4.8)
Site unknown[b]	13 (0.8)	17 (1.0)

CRC, colorectal cancer.
[a]Patients with anal cancer (International Classification of Diseases, 10th Revision code C21) were excluded.
[b]International Classification of Diseases, 10th Revision code C18.9.

pronounced with increasing stage. For stage IV CRC, the IRR was 0.28. Attendance was associated with a decreased risk of disease irrespective of site, although the IRR vs non-attendance was 0.78 for proximal colon, 0.62 for distal colon, and 0.57 for the rectum.

In general, women attending the screening program experienced smaller CRC incidence changes, but the pattern was the same as for men. The overall decrease was 25%. There was a larger excess incidence of stage I lesions, 64%, and comparable decreases for higher tumor stage categories. The overall IRR for both sexes combined was 0.69 (95% CI, 0.66−0.72).

A sensitivity analysis was performed by excluding from non-attenders those subjects (men, n = 164; women, n = 102) with potentially prevalent CRC who did not respond to the first invitation and were diagnosed with the disease during the next 6 months. The IRR increased to 0.70 (95% CI, 0.66−0.74) among men and 0.80 (95% CI, 0.75−0.86) among women.

The ratio between the cumulative incidence among attenders and that observed in the whole cohort of people invited –a measure of the decrease in overall incidence in the target population– was 0.81 (95% CI, 0.77−0.85) for men, 0.88 (95% CI, 0.83−0.93) for women.

Adjustment for Self-Selection

The ratio between the number of CRC cases observed among non-attenders and that expected based on pre-screening incidence rates was 1.03 (95% CI, 0.99−1.07) for men and 1.06 (95% CI, 1.00−1.11) for women. By implication, the estimated IRRs suffered from a self-selection bias of borderline significance. The overall self-selection-adjusted IRR rose from 0.65 to 0.67 (95% CI, 0.62−0.72) for men, and from 0.75 to 0.79 (95% CI, 0.72−0.88) for women. Given this limited degree of self-selection, adjusted age-, tumor stage-, and tumor site-specific IRRs are not presented here.

Incidence-based CRC Mortality Rates and Rate Ratios

Supplementary Figure 4 shows that attenders of both sexes experienced lower cumulative incidence-based CRC mortality rates than non-attenders with virtually no latency time to the divergence of the 2 curves.

Table 3 shows the comparison of incidence-based cause-specific mortality rates. Among men, the impact of attendance was more pronounced than the impact on incidence, with an overall MRR of 0.32. There were modest age-related differences. The MRR was lower for stage IV CRC. The effectiveness of FIT screening was confirmed to be less against the lesions located in the proximal colon.

For women, the pattern of results was very similar but with MRRs generally higher. The overall figure was 0.40. The overall MRR for both sexes combined was 0.35 (95% CI, 0.31−0.39). The self-selection-adjusted MRR rose to 0.35 (95% CI, 0.29−0.41) for men and 0.46 (95% CI, 0.37−0.58) for women.

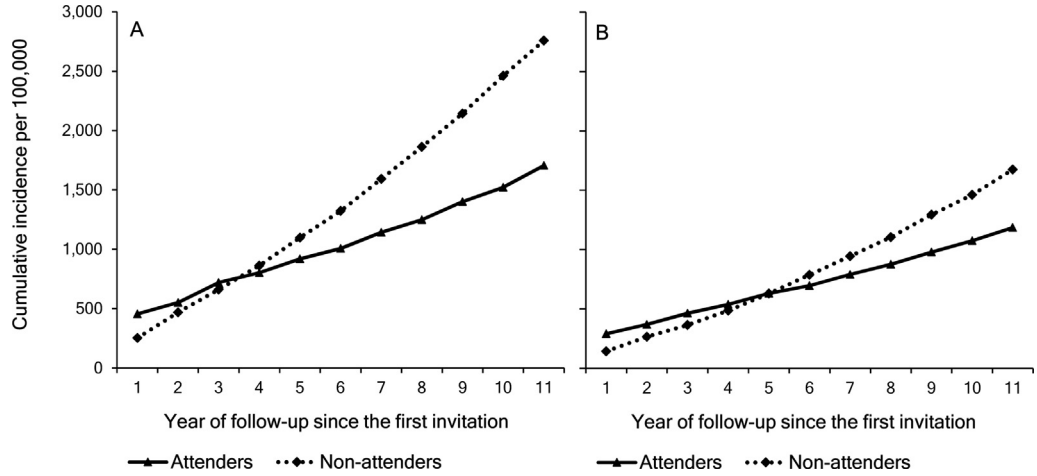

Figure 1. Curve of cumulative age-standardized colorectal cancer (CRC) incidence rates among attenders and non-attenders to the Emilia-Romagna Region (northern Italy) CRC biennial FIT screening program (year of start, 2005) during 11 years of follow-up since the first invitation, by sex (*A*, men; *B*, women).

All-cause, non-CRC-related Mortality

All-cause, non-CRC-related MRR was 0.45 (95% CI, 0.44−0.47) for men and 0.43 (95% CI, 0.41−0.44) for women. After excluding those subjects who died within 90 days since the date of the first invitation (n = 804), the figure increased to 0.46 (95% CI, 0.45−0.48) and 0.44 (95% CI, 0.42−0.45).

Discussion

The above results can be summarized as follows. The annual incidence of CRC among attenders peaked in year 1 since the first invitation and, subsequently, remained always below the rate observed among non-attenders. The cumulative incidence was higher among attenders for about 4 to 5 years, after which the rate began to be

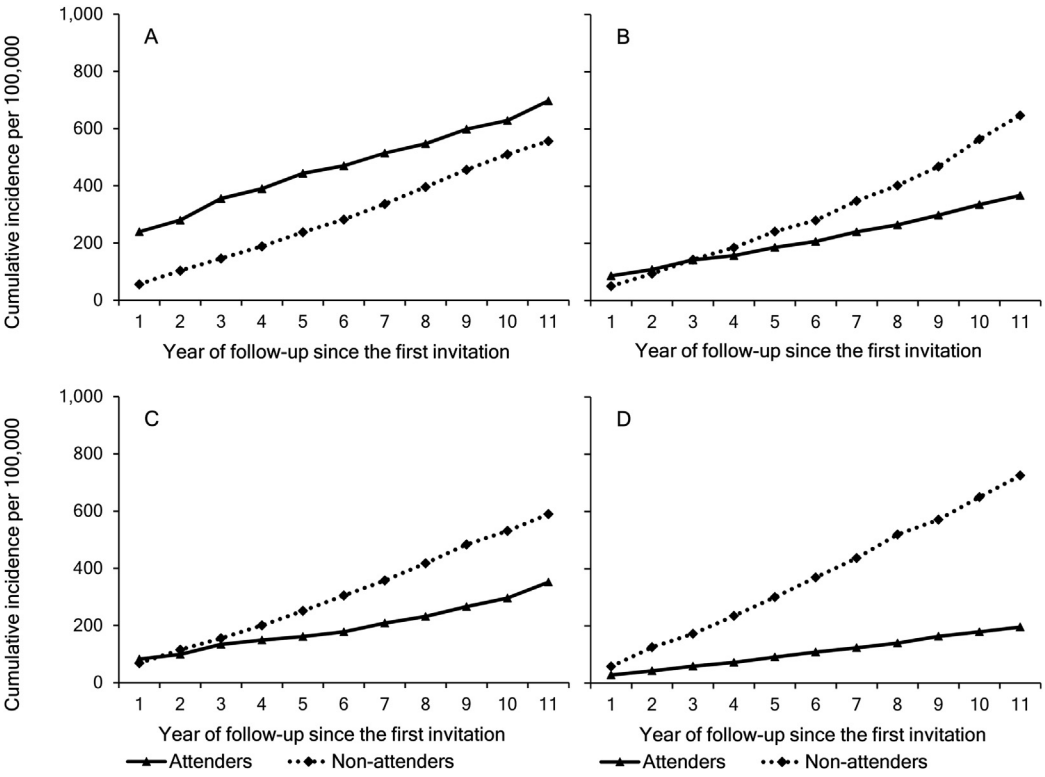

Figure 2. Curve of cumulative age-standardized colorectal cancer (CRC) incidence rates among men attending and non-attending to the Emilia-Romagna Region (northern Italy) CRC biennial FIT screening program (year of start, 2005) during 11 years of follow-up since the first invitation, by TNM stage (*A*, stage I; *B*, stage II; *C*, stage III; *D*, stage IV).

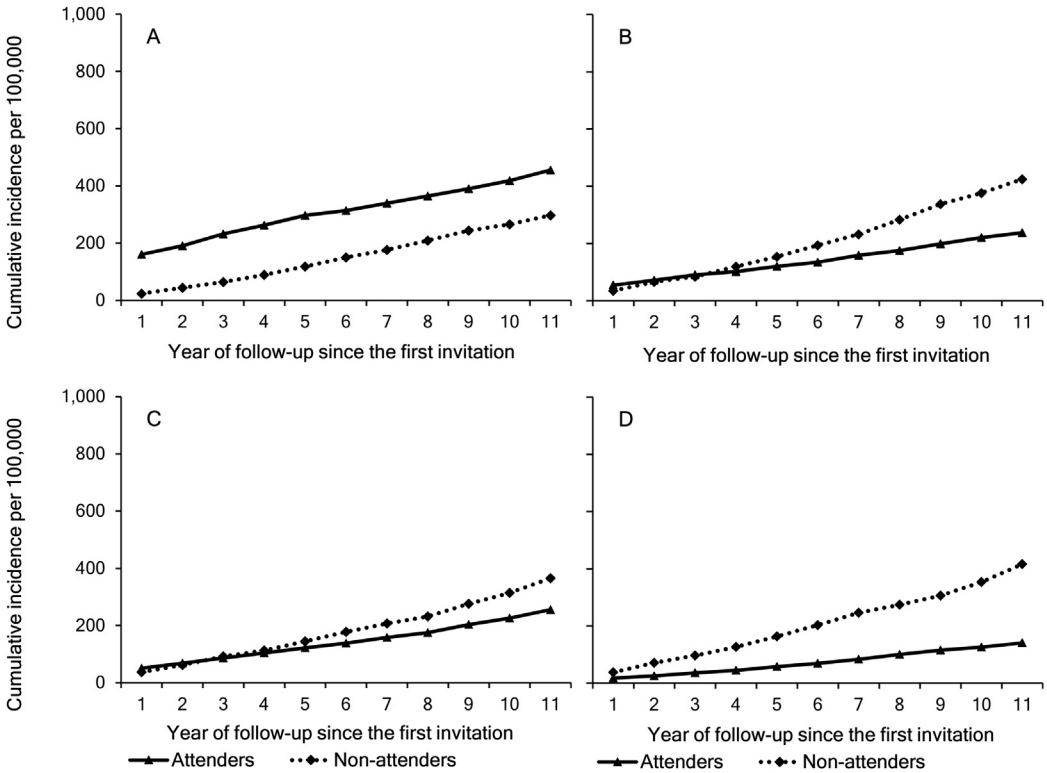

Figure 3. Curve of cumulative age-standardized colorectal cancer (CRC) incidence rates among women attending and non-attending to the Emilia-Romagna Region (northern Italy) CRC biennial FIT screening program (year of start, 2005) during 11 years of follow-up since the first invitation, by TNM stage (*A*, stage I; *B*, stage II; *C*, stage III; *D*, stage IV).

increasingly lower. The impact on cumulative incidence had a decreasing latency with increasing tumor stage, reflecting the shorter lead time of advanced-stage diseases. At 11 years of follow-up, attenders experienced an overall incidence decrease varying from 33% (men) to 21% (women). The decrease was more pronounced with increasing tumor stage. The incidence-based CRC mortality dropped by 65% (men) to 54% (women).

In our opinion, interpreting these findings is straightforward. The peak in annual CRC incidence in year 1, the rapid decrease occurring soon after, the similarity between the changes in cumulative incidence and those reported in some previous studies of varying design,[10,13,19] the perfect overlap between the time pattern of changes in cumulative incidence and those observed in sigmoidoscopy trials, with an equal latency time of 4 to 5 years,[1-3] the inverse relationship of these changes with tumor stage, and the observation that the reduction in incidence-based CRC mortality followed the same sex-, age-, tumor stage-, and tumor site-specific pattern as the reduction in incidence point to the comprehensive interpretation that these findings are the consequence of exposure to FIT screening.

With respect to the smaller effect on incidence being observed among women, we relate it to a lower sensitivity of FIT. This has already been demonstrated in the Emilia-Romagna Region screening program.[17] In the current study, women also showed a longer latency time to the incidence decrease, which suggests that the average lead time of screen-prevented CRCs is longer. To explain both findings, a unifying hypothesis is that women are affected by clinically more indolent adenomas with less common bleeding and slower progression.

We observed a smaller CRC risk reduction for women irrespective of tumor site as well as subject age. Thus, we cannot confirm the results of a pooled analysis of flexible sigmoidoscopy trials reported by Holme et al.[20] In their data, screening reduced CRC incidence to a similar extent for men and women in the distal colon but not in the proximal colon, where there was no effect for older women.

The finding that the effect on CRC mortality rates was larger than the effect on incidence was expected.[1,10,13] It clearly indicates that FIT screening prevents deaths both through the removal of high-risk adenomas and through effective treatment of earlier screen-detected invasive CRCs. Equally expected was that the mortality decrease, unlike the impact on cumulative incidence, had virtually no latency time. This is because the screening process brings about an early and transient peak in incidence but not in mortality.

Our data corroborate the few previous observational longitudinal studies on the effectiveness of FIT screening in reducing CRC incidence. Two small Italian studies showed significant reductions of about 20%.[11,12] In the study by Levin et al, the decrease was estimated at 25%.[13] In the Taiwanese FIT screening program,

Table 2. Age-standardized CRC Incidence Rate for, and Incidence Rate Ratio Between, Attenders and Non-attenders to the Emilia-Romagna Region (Northern Italy) CRC Biennial FIT Screening Program (Year of Start, 2005) During 11 Years of Follow-up Since the First Invitation, by Sex, Patient Age, Tumor Stage, and Tumor Site

	Age-standardized[a] rate		IRR (95% CI) for attenders vs non-attenders[b]
	Attenders	Non-attenders	
Sex			
Men	156.4	242.2	0.65 (0.61–0.69)
Women	109.3	145.8	0.75 (0.70–0.80)
Men			
Age, *y*			
50–54	64.0	91.6	0.70 (0.61–0.80)
55–59	131.5	199.9	0.66 (0.58–0.75)
60–64	191.9	321.5	0.60 (0.53–0.67)
65–69	264.7	397.1	0.67 (0.60–0.74)
Tumor stage[c]			
I	65.0	50.2	1.35 (1.20–1.50)
II	33.9	55.6	0.61 (0.53–0.69)
III	31.2	52.8	0.60 (0.53–0.68)
IV	17.9	64.0	0.28 (0.24–0.32)
Total III–IV	49.1	116.8	0.42 (0.38–0.47)
Tumor site[c]			
Proximal colon	57.1	73.9	0.78 (0.70–0.86)
Distal colon	55.3	89.7	0.62 (0.56–0.68)
Rectum	40.6	72.4	0.57 (0.51–0.64)
Women			
Age, *y*			
50–54	56.7	76.1	0.75 (0.65–0.86)
55–59	98.6	141.9	0.69 (0.60–0.81)
60–64	125.0	164.7	0.76 (0.66–0.88)
65–69	171.6	218.6	0.79 (0.70–0.88)
Tumor stage[c]			
I	43.0	26.3	1.64 (1.43–1.89)
II	22.1	37.0	0.60 (0.52–0.69)
III	23.2	31.8	0.73 (0.63–0.85)
IV	12.7	35.9	0.35 (0.30–0.42)
Total III–IV	35.9	67.7	0.53 (0.48–0.59)
Tumor site[c]			
Proximal colon	45.3	51.6	0.88 (0.78–0.98)
Distal colon	37.3	47.9	0.76 (0.68–0.86)
Rectum	22.1	38.2	0.60 (0.52–0.69)

Note: Follow-up was truncated at 11 years, representing the 75th percentile of available follow-up times.
CRC, colorectal cancer; *CI*, confidence interval; *FIT*, fecal immunochemical test; *IRR*, incidence rate ratio.
[a]Using the 2013 European standard population.
[b]Controlling for age at the first invitation.
[c]Patients with anal cancer (International Classification of Diseases,10th Revision code C21) were excluded.

Table 3. Age-standardized Incidence-Based CRC Mortality Rate for, and Mortality Rate Ratio Between, Attenders and Non-attenders to the Emilia-Romagna Region (Northern Italy) CRC Biennial FIT Screening Program (year of start, 2005) During 11 Years of Follow-up Since the First Invitation, by Sex, Age, Tumor Stage, and Tumor Site

	Age-standardized[a] mortality rate (number of deaths)		MRR (95% CI) for attenders vs non-attenders[b]
	Attenders (n = 469)	Non-attenders (n = 1038)	
Sex			
Men	20.3 (257)	63.6 (651)	0.32 (0.28–0.37)
Women	14.0 (212)	35.5 (387)	0.40 (0.34–0.47)
Men			
Age, y			
50–54	6.2 (34)	21.4 (123)	0.29 (0.20–0.42)
55–59	16.1 (48)	51.2 (123)	0.31 (0.22–0.44)
60–64	22.6 (61)	78.8 (154)	0.29 (0.21–0.39)
65–69	40.7 (114)	115.3 (251)	0.35 (0.28–0.44)
Tumor stage[c]			
I	1.6 (21)	1.5 (14)	1.21 (0.61–2.37)
II	2.1 (27)	4.4 (43)	0.49 (0.30–0.80)
III	5.1 (63)	10.2 (102)	0.49 (0.36–0.67)
IV	10.4 (132)	42.6 (438)	0.24 (0.20–0.30)
Total III–IV	15.4 (195)	52.8 (540)	0.29 (0.25–0.34)
Tumor site[c]			
Proximal colon	8.8 (112)	18.3 (184)	0.49 (0.39–0.62)
Distal colon	5.1 (64)	22.2 (227)	0.23 (0.17–0.30)
Rectum	5.8 (74)	20.9 (217)	0.28 (0.21–0.36)
Women			
Age, *y*			
50–54	5.3 (35)	14.6 (78)	0.36 (0.24–0.54)
55–59	10.1 (37)	33.9 (79)	0.30 (0.20–0.44)
60–64	14.0 (44)	41.5 (85)	0.34 (0.23–0.49)
65–69	29.6 (96)	57.2 (145)	0.52 (0.40–0.67)
Tumor stage[c]			
I	0.5 (8)	0.3 (3)	1.86 (0.49–7.01)
II	1.3 (19)	3.5 (37)	0.37 (0.21–0.65)
III	3.0 (47)	5.0 (54)	0.64 (0.44–0.95)
IV	7.9 (120)	22.9 (251)	0.35 (0.28–0.43)
Total III-IV	11.0 (167)	27.9 (305)	0.40 (0.33–0.48)
Tumor site[c]			
Proximal colon	6.9 (103)	12.4 (134)	0.56 (0.43–0.72)
Distal colon	3.5 (54)	10.6 (118)	0.33 (0.24–0.46)
Rectum	3.1 (48)	10.0 (106)	0.33 (0.23–0.46)

Note: Because none of the people in the cohort had had a diagnosis of CRC before the date of their first invitation to screening, incidence-based mortality rates included only those deaths occurring in people already targeted for screening, with CRC diagnosed after their first invitation. Follow-up was truncated at 11 years for uniformity with the analysis of incidence.
CRC, colorectal cancer; *CI*, confidence interval; *FIT*, fecal immunochemical test; *MRR*, mortality rate ratio.
[a]Using the 2013 European standard population.
[b]Controlling for age at the first invitation.
[c]Patients with anal cancer (International Classification of Diseases, 10th Revision code C21) were excluded.

long-term results have shown a 34% reduction in the incidence of advanced-stage CRC.[15] Total incidence data have yet to be evaluated.

There are some methodological strengths in this study. For example, the large sample size enabled us to perform subgroup analyses. The findings regarding the magnitude and time pattern of changes in CRC incidence by tumor stage were particularly illustrative of the effects of FIT screening. Another major characteristic of the design was that the follow-up period was coincident with the accrual period and, thus, the analysis of

incidence-based mortality was free of the lead time bias that arises when follow-up continues after the end of accrual.[21]

This study also has limitations needing attention. First, we classified the pattern of attendance based solely on the first 2 invitations, but both attenders and non-attenders were subsequently re-invited from once to 5 times. The degree of mutual contamination between the 2 populations, however, was low. It must also be noted that the associated misclassifications led to a bias towards the null hypothesis of no difference in CRC incidence between attenders and non-attenders.

Second, attenders were at slightly decreased risk of CRC compared with the pre-screening population, which indicates a lower prevalence of risk factors for the disease. After we accounted for this limited degree of self-selection, the IRR rose from 0.65 to 0.67 for men and from 0.75 to 0.79 for women. The method we used to make allowance for self-selection was proposed by Puliti et al[18] and, albeit comparatively simple, has analogies with the approach used by Chiu et al.[14]

Third, we found a considerable difference in all-cause, non-CRC-related mortality between attenders and non-attenders. There are 2 aspects to consider. On the one hand, barriers to participation in CRC screening include fatalism, low education, low income, poor health information and knowledge, and negative attitudes towards cancer screening.[22] On the other hand, non-attenders to CRC screening are characterized by a higher likelihood of having overweight, obesity, and type 2 diabetes,[23] which increase the risk of a large spectrum of high-incidence cancers (particularly of the breast and prostate) and cardiovascular diseases. The interaction between a passive health behavior and this epidemiologic pattern provides an explanation for the difference in non-CRC-related mortality between attenders and non-attenders. This observation is important because, for attenders, a high life expectancy moderates their risk of overdiagnosis and offers more years of life saved.

And fourth, it remains necessary to evaluate other major issues of the program. In particular, we have planned to monitor the adherence to post-colonoscopy surveillance of subjects diagnosed with advanced adenoma,[24] and to conduct an intention-to-screen study to assess the impact on CRC incidence in the whole target population. As regards the latter, a promising observation reported here is that the ratio between the cumulative incidence among attenders and that observed in whole cohort was significantly below the unity.

In conclusion, the results of this study add another piece of evidence for the effectiveness of FIT screening in reducing CRC incidence and mortality.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2022.01.053.

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Conflicts of interest
The authors disclose no conflicts.