Results of Compliant Participation in Five Rounds of Fecal Immunochemical Test Screening for Colorectal Cancer

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BACKGROUND & AIMS: **We investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second and subsequent rounds.**

METHODS: **We followed up 494,187 participants from the first round of a regional biennial FIT screening program in Italy (cut-off value for positivity, 20 μg hemoglobin/g feces) for 5 total rounds (2005–2016). At each round, only compliant participants were eligible. Performance measures from the first, third, fourth, and fifth round were compared with those from the second round (the first incidence round) using rate ratios from multivariate Poisson regression models and relative risk ratios from multinomial logistic regression models.**

RESULTS: **Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men with a positive FIT result (from 5.2% to 4.3%) and in detection rates of advanced adenoma (from 13.4 to 10.2 per 1000), CRC (from 1.7 to 1.4 per 1000), and advanced neoplasia (from 15.1 to 11.6 per 1000). Positive predictive values (PPVs) decreased by 10% or less between the second and third rounds. Detection rates and PPVs for adenoma stabilized by the fourth and fifth rounds. The PPVs for advanced adenoma, CRC, and advanced neoplasia decreased slightly in men and women by the fourth and fifth rounds. The detection rate of proximal colon cancer stabilized after the second round, whereas the detection rate of distal CRC decreased until the fourth round in men (from 0.7 to 0.3 per 1000), and the fifth round in women.**

CONCLUSIONS: **These findings support the notion that FIT screening prevents progression of a subset of advanced adenomas. Screening intensity could be modulated based on results from previous rounds, with a risk-based strategy.**

Keywords: Colon Cancer; Adenoma; Neoplasm; Early Detection.

Several studies have reported that the main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC), in particular the proportion of positive FIT results, their positive predictive value (PPV), and the yield of disease, show a marked decrease after the first screening round.[1–8] This is of interest from many points of view: the communication of benefits and harms of the screening process to invited people, the planning of endoscopy services, and the development of risk-based screening strategies.

Abbreviations used in this paper: **CRC, colorectal cancer; DR, detection rate; FIT, fecal immunochemical test; PPV, positive predictive value.**

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However, it is unclear whether the decrease continues for certain performance measures after the second round. This depends, first, on the varying design of the relevant studies. In general, the authors defined a screening round as a complete cycle of invitations, during which the whole target population was invited.[1–5,8] Under this design, all participants in any given round were evaluated irrespective of their participation in previous rounds. For example, subjects who responded to an invitation after 2 refusals contributed to the results of the third screening round, although they were actually at their prevalence round. In 2 studies, conversely, only subjects with compliant participation to previous rounds were considered eligible.[6,7] Subjects participating in the third round, for example, were eligible only if they also had participated in the first 2 rounds.

Second, most studies had a small size and covered limited observation times. Some studies considered only the first 2 rounds.[2,5] In a study covering 6 rounds, the proportion of positive FIT results, the detection rate (DR) of advanced adenoma, and the PPV for advanced adenoma decreased between the first and the second round, and then stabilized. The DR of CRC, instead, continued to decrease, with a DR ratio of the sixth round to the first round as low as 0.18.[7]

Third, most previous studies did not make an allowance for the aging of the population, which is associated with increasing risk of disease. This explains, for example, the increase in the proportion of positive FIT results and the DR of advanced neoplasia that was observed at the fourth round of a screening trial.[8]

This article describes a large study of this issue, which aimed to evaluate the performance of compliant participation in the first 5 rounds of a biennial FIT screening program in Italy.

What You Need to Know

Background

Little is known about the magnitude and temporal patterns of the decreasing trends in main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer that have been observed in second and subsequent rounds.

Findings

Findings from the study support the concept that FIT screening prevents progression of a subset of advanced adenomas. Screening intensity could be modulated based on results from previous rounds, with a risk-based strategy.

Implications for patient care

FIT screening strategies for colorectal cancer might be designed specifically for each patient based on results from previous rounds of screening.

Materials and Methods

Setting

In the Emilia-Romagna Region (northern Italy), a population-based CRC screening program has been ongoing since March 2005. The target population includes the residents of both sexes ages 50 to 69 years (n = 1,037,532 on January 1, 2005). The program is run at the health care district level (n = 11) according to a standard protocol.

Every 2 years, eligible subjects are invited with a personal letter to perform a single-sample FIT. Most kits are distributed by public pharmacies and primary care facilities.[9] Nonresponders to the invitation are mailed a reminder, usually within 6 months. The screening test is a latex agglutination test (OC-Sensor; Eiken Chemical Co, Tokyo, Japan) without dietary restrictions. The cut-off value for positivity is 20 μg hemoglobin/g feces (100 ng hemoglobin/mL of buffer). Subjects are notified of negative FIT results by mail. Subjects with positive results are contacted by telephone, invited to attend a screening center, and referred for complete conventional colonoscopy under sedation. In the case of incomplete colonoscopy, patients are presented with the option of a virtual colonoscopy. Patients with positive FIT results and a negative colonoscopic assessment are re-invited to a FIT screening 5 years later.

Objectives and Design

The study had a cohort design. The objectives were to contrast the performance measures of FIT screening at each of the first 5 rounds in a population of compliant participants with the average measures observed in the total screening population, and to investigate the decrease observed among compliant participants by comparing the third, fourth, and fifth round with the second round (ie, the first incidence round).

Regarding compliant participants, the performance measures were calculated cross-sectionally, for 5 rounds, in a cohort of subjects including all residents ages 50 to 69 years who were invited and had a FIT during the first round of the screening program. The dates of FITs varied between March 21, 2005, and December 31, 2016. A compliant participant was defined as one who had 2, 3, 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). The follow-up evaluation of each FIT ceased on the date of the following events, whichever came first: last regular FIT; receipt of colonoscopy for a positive FIT result; screening cessation (at age 70 y); migration; and death. Colonoscopies performed within 1 year of a positive FIT result and surgical treatments performed within 1 year of a positive colonoscopy were considered part of a single screening episode. The last date of follow-up evaluation of positive FIT results was December 31, 2018.

Table 1. Total Screening Population: Number of Subjects Invited to and Participating in Five Organizational Screening Rounds, the Number of Subjects With Positive FIT Results, of Subjects Undergoing Colonoscopic Assessment, of Subjects With Successful Cecal Intubation, and of Subjects Diagnosed With Colorectal Adenoma and Colorectal Cancer, by Sex and Screening Round

	Males					Females				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Invited	405,639	477,656	489,301	521,819	525,698	439,466	512,661	529,538	562,309	565,873
Participating	183,503	229,254	244,577	258,001	261,179	214,941	266,779	283,270	299,020	302,663
With positive FIT results	13,108	14,397	12,170	12,140	13,370	9974	11,491	10,176	10,505	11,893
With colonoscopic assessment	10,397	11,496	9967	9840	10,624	7586	8792	8188	8379	9301
With successful cecal intubation	9853	11,053	9445	9487	10,289	7015	8382	7732	8100	8969
With adenoma										
Advanced adenoma	4062	3729	3218	3063	2930	2160	2046	1843	1786	1754
Total adenoma	5668	5907	5014	4710	4784	3082	3296	3000	2835	2899
With colorectal cancer[a]										
Stage I	383	313	198	152	139	252	188	126	115	109
Stage II	136	90	81	59	48	73	66	62	46	47
Stage III	145	119	66	72	53	98	88	69	72	51
Stage IV[a]	NA	5	9	12	11	NA	2	8	7	4
Stage unknown	191	69	55	41	59	89	35	36	27	28
Total colorectal cancer	855	596	409	336	310	512	379	301	267	239
With advanced neoplasia[b]	4917	4325	3627	3399	3240	2672	2425	2144	2053	1993

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005–2014).
FIT, fecal immunochemical test; NA, not available.
[a]During the first screening round, data for stage IV colorectal cancer in the total screening population were not collected.
[b]Advanced neoplasia indicates advanced adenoma and colorectal cancer.

With respect to the total screening population, the performance measures of screening were calculated in five 2-year screening rounds (organizational rounds). The population was treated as an open cohort.

Data Sources

With respect to the total screening population, study data were taken from the annual national surveys conducted by the National Centre for Screening Monitoring, which collects standard data from local screening units. Data on the detection of CRC by disease site were not collected.

Data for compliant participants were obtained from the Information System for the Surveillance of Colorectal Screening (*flusso informativo Screening Colon-Retto*) of the Department of Health of the Regional Administration. Every 4 months, each health care district screening unit provides electronic records for all subjects in the target population. The System is an anonymous relational database created by record-linking multiple data sets (population list, invitations, FITs, colonoscopies, diagnoses, surgical treatments, and vital status). The findings of each screening episode are classified as follows: CRC, advanced adenoma (≥1 cm in diameter, or villous/tubulovillous type, or with high-grade dysplasia), nonadvanced adenoma, or negative. In the case of CRC, tumor stage and disease site were recorded. Tumor stage was classified according to the American Joint Committee on Cancer TNM staging system, sixth edition. Disease site was classified as the proximal colon (from the cecum to the transverse colon), distal colon (from the splenic flexure to the sigmoid colon), and rectum (rectosigmoid junction and rectum).[10] Because a successful cecal intubation was achieved in a proportion of patients close to 100%, this information was not included in the download file.

Performance Measures

The primary study end points included the following performance measures: (1) the proportion of positive FIT results (ie, the percentage of subjects with a completed FIT who had a positive result); (2) the DR of advanced adenoma, CRC, and advanced neoplasia (including CRC and advanced adenoma) (ie, the proportion of subjects with a completed FIT who were diagnosed with these lesions per 1000 screenees); and (3) the PPV for adenoma (also referred to as the adenoma detection rate),[11] advanced adenoma, CRC, and advanced neoplasia at colonoscopy (ie, the percentage of subjects undergoing colonoscopy who were diagnosed with nonadvanced/advanced adenoma, advanced adenoma, CRC, and advanced neoplasia).

Statistical Analysis

Analysis was truncated at the fifth screening round because the length of follow-up evaluation available in the case of positive FIT results in the sixth round was insufficient for more than 50% of subjects.

Table 2. Total Screening Population: Participation Rate, Proportion of Positive FIT Results, Colonoscopic Assessment Rate, Successful Cecal Intubation Rate, DR of Colorectal Adenoma and Colorectal Cancer, and PPV for Colorectal Adenoma and Colorectal Cancer, by Sex and Screening Round

	Males					Females				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Participation rate, %	45.2	48.0	50.0	49.4	49.7	48.9	52.0	53.5	53.2	53.5
Proportion of positive FIT results, %	7.1	6.3	5.0	4.7	5.1	4.6	4.3	3.6	3.5	3.9
Colonoscopic assessment rate, %	79.3	79.8	81.9	81.1	79.5	76.1	76.5	80.5	79.8	78.2
Successful cecal intubation rate, %	94.8	96.1	94.8	96.4	96.8	92.5	95.3	94.4	96.7	96.4
DR of advanced adenoma (per 1000)	22.1	16.3	13.2	11.9	11.2	10.0	7.7	6.5	6.0	5.8
DR of colorectal cancer (per 1000)	4.7	2.6	1.7	1.3	1.2	2.4	1.4	1.1	0.9	0.8
DR of advanced neoplasia[a] (per 1000)	26.8	18.9	14.8	13.2	12.4	12.4	9.1	7.6	6.9	6.6
PPV for adenoma,[b] %	54.5	51.4	50.3	47.9	45.0	40.6	37.5	36.6	33.8	31.2
PPV for advanced adenoma, %	39.1	32.4	32.3	31.1	27.6	28.5	23.3	22.5	21.3	18.9
PPV for colorectal cancer, %	8.2	5.2	4.1	3.4	2.9	6.7	4.3	3.7	3.2	2.6
PPV for advanced neoplasia, %	47.3	37.6	36.4	34.5	30.5	35.2	27.6	26.2	24.5	21.4
DR of stage I colorectal cancer (per 1000)	2.1	1.4	0.8	0.6	0.5	1.2	0.7	0.4	0.4	0.4
DR of stage II colorectal cancer (per 1000)	0.7	0.4	0.3	0.2	0.2	0.3	0.2	0.2	0.2	0.2
DR of stage III colorectal cancer (per 1000)	0.8	0.5	0.3	0.3	0.2	0.5	0.3	0.2	0.2	0.2
DR of stage IV colorectal cancer (per 1000)[c]	NA	<0.1	<0.1	<0.1	<0.1	NA	<0.1	<0.1	<0.1	<0.1

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005–2014). The participation rate is per 100 subjects invited. The proportion of positive FIT results is per 100 subjects undergoing FIT screening. The colonoscopic assessment rate is per 100 subjects with positive FIT results. The successful cecal intubation rate is per 100 subjects with positive FIT results undergoing colonoscopic assessment. The DRs of advanced adenoma, colorectal cancer, and advanced neoplasia are per 1000 subjects undergoing FIT screening. The PPVs are per 100 subjects with positive FIT results undergoing colonoscopic assessment. Anal cancer cases were excluded from the DR of colorectal cancer by tumor stage.
DR, detection rate; FIT, fecal immunochemical test; NA, not available; PPV, positive predictive value.
[a]Advanced neoplasia indicates advanced adenoma and colorectal cancer.
[b]Also referred to as the adenoma detection rate.
[c]During the first screening round, data for stage IV colorectal cancer in the total screening population were not collected.

Multivariate Poisson regression models were built to estimate the rate ratio, with 95% CIs, for the association between the screening round and each of the earlier-described performance measures. The second round was used as a reference category.

Further analyses were restricted to the DR of CRC. Multinomial logistic models were built to estimate the probability of detection of CRC by disease site and tumor stage compared with no detection. The probability was expressed as a relative risk ratio, with 95% CIs, using the second screening round as a reference category. Anal cancer cases were excluded from the estimate of the probability of detection of CRC by disease site and tumor stage. All models were adjusted for age.

All analyses were performed using SAS Enterprise Guide (version 5.1; SAS Institute, Inc, Cary, NC) and STATA (version 15.1, Stata Corporation, College Station, TX).

This study received Institutional Review Board approval from the Romagna Cancer Institute (protocol ID, L1P2043).

Results

Total Screening Population

Table 1 shows the absolute numbers of all subjects who were invited to screening, who participated, who tested positive, and who were diagnosed with adenoma and CRC in 5 organizational screening rounds. The resulting performance measures are shown in Table 2.

Compliant Participants: Numbers and Rates

Tables 3 to 6 consider only compliant participants. Table 3 provides their absolute numbers as well as the numbers of subjects with positive FIT results and with screen-detected disease.

Table 4 shows the performance measures under study, namely, the participation rate, the proportion of positive FIT results, the colonoscopic assessment rate, the DR of (and the PPV for) adenoma, advanced adenoma, CRC, and advanced neoplasia, and the DR of CRC by disease site and tumor stage. Contrasting these data with those from the total screening population, the second and subsequent rounds among compliant participants of both sexes were characterized by a smaller proportion of positive FIT results and a generally lower DR of advanced adenoma. The PPVs for advanced adenoma and advanced neoplasia also were lower.

Compliant Participants: Trends Across Rounds

Table 5 shows the rate ratios for the association between the screening round and the main of the earlier- Q17 described measures. The expected decrease between

Table 3. Compliant Participants: Number of Subjects Eligible to, Invited to, and Participating in Five Screening Rounds, Number of Subjects With Positive FIT Results, Undergoing Colonoscopic Assessment, With Successful Cecal Intubation, and Diagnosed With Colorectal Adenoma and Colorectal Cancer, by Sex and Screening Round

	Males					Females				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Eligible	501,826	215,681	129,396	97,675	72,054	535,706	254,292	154,635	118,134	88,491
Invited	474,319	176,420	110,717	82,133	60,260	508,912	208,163	133,226	100,116	74,713
Participants	229,742	135,508	101,506	76,941	57,041	264,445	159,644	121,662	93,454	70,437
With positive FIT results	16,434	7024	4339	3375	2686	12,244	5909	4017	3198	2695
With colonoscopic assessment	14,061	6112	3831	3039	2353	10,153	5009	3528	2820	2340
With successful cecal intubation	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
With adenoma										
Advanced adenoma	5726	1819	1034	848	592	3099	1024	651	509	402
Total adenoma	7912	3022	1779	1451	1078	4350	1731	1174	941	770
With colorectal cancer										
Proximal colon	222	70	58	42	37	152	71	68	37	44
Distal colon	600	99	47	24	22	362	53	40	24	13
Rectum	229	62	39	38	23	110	44	26	16	15
Anus[a]	2	1	0	1	2	2	2	0	0	0
Site unknown	1	0	0	0	0	2	0	0	0	0
Stage I	572	114	78	54	42	346	79	54	38	36
Stage II	196	47	35	17	17	106	27	26	16	10
Stage III	184	46	21	22	13	133	55	39	21	17
Stage IV	42	7	2	2	3	13	2	6	0	1
Stage unknown	58	17	8	9	7	28	5	9	2	8
Total colorectal cancer	1054	232	144	105	84	628	170	134	77	72
With advanced neoplasia[b]	6780	2051	1178	953	676	3727	1194	785	586	474

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005–2016). A compliant participant was defined as one who had 2, 3, 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). A total of 1848 males and 2143 females with negative FIT results in the fourth screening round were considered not eligible for the fifth round because the length of follow-up time available in the case of positive FIT results was insufficient. The discrepancy between the number eligible and the number invited in each round is accounted for by subjects who died or migrated before invitation, subjects who were invited or re-invited at age 70 or older, and subjects who were re-invited more than 2.5 years after the previous negative FIT.
FIT, fecal immunochemical test; NA, not available.
[a]Anal cancer cases were excluded from the number of cases by tumor stage.
[b]Advanced neoplasia indicates advanced adenoma and colorectal cancer.

the first and the second round was confirmed for all of these, with the exception of the colonoscopic assessment rate. Between the second and the third round, a further 20% to 30% decrease was observed for males in the proportion of positive FIT results and in all DRs. PPVs decreased by 10% or less. Among females, these measures decreased to a lesser extent.

At the fourth and fifth round, the DRs and the PPV for adenoma stabilized. Conversely, a further, albeit limited, decrease was observed for both sexes in the PPV for advanced adenoma, colorectal cancer, and advanced neoplasia. The tests for interaction between sex and screening round confirmed that the downward trend in most measures was more pronounced for males.

In Table 6, the relative risk ratios for the association between the screening round and the DR of CRC by disease site and tumor stage are shown. For both sexes, the DR of proximal colon cancer did not change further after the second round, whereas the yield of distal disease continued to decrease until the fourth (males) and fifth (females) rounds. This observation should be related to the fact that the DR of proximal colon cancer, after plateauing, remained at a higher absolute level than that of distal colon cancer, especially among females (Table 4). Regarding tumor stage, the DR of stage I and stage II CRC stabilized, for both sexes, only at the fourth round.

Discussion

Compared with the total screening population, compliant participants in the second and subsequent screening rounds had a lower proportion of positive FIT results and generally lower values for the DR of advanced adenoma and the PPV for advanced adenoma and advanced neoplasia. Data for organizational screening rounds refer to total participants, including subjects at their first FIT and subjects with occasional participation who had a screening interval longer than the standard. The prevalence of preclinical disease was higher in never-screened subjects and, albeit lower, increased with increasing screening intervals among ever-screened subjects. Thus, the earlier-described findings were expected.

With respect to compliant participants, the length of follow-up evaluation and the epidemiologic background of this study are comparable with the 2 complementary

Table 4. Compliant Participants: Participation Rate, Proportion of Positive FIT Results, Colonoscopic Assessment Rate, Successful Cecal Intubation Rate, DR of Colorectal Adenoma and Colorectal Cancer, and PPV for Colorectal Adenoma and Colorectal Cancer, by Sex and Screening Round

	Round				
	1st	2nd	3rd	4th	5th
Males					
Participation rate, %	48.4	76.8	91.7	93.7	94.7
Proportion of positive FIT results, %	7.2	5.2	4.3	4.4	4.7
Colonoscopic assessment rate, %	85.6	87.0	88.3	90.0	87.6
Successful cecal intubation rate, %	NA	NA	NA	NA	NA
DR of advanced adenoma (per 1000)	24.9	13.4	10.2	11.0	10.4
DR of colorectal cancer (per 1000)	4.6	1.7	1.4	1.4	1.5
DR of advanced neoplasia[a] (per 1000)	29.5	15.1	11.6	12.4	11.9
PPV for adenoma,[b] %	56.3	49.4	46.4	47.7	45.8
PPV for advanced adenoma, %	40.7	29.8	27.0	27.9	25.2
PPV for colorectal cancer, %	7.5	3.8	3.8	3.5	3.6
PPV for advanced neoplasia,[a] %	48.2	33.6	30.7	31.4	28.7
DR of proximal colon cancer (per 1000)	1.0	0.5	0.6	0.5	0.6
DR of distal colon cancer (per 1000)	2.6	0.7	0.5	0.3	0.4
DR of rectal cancer (per 1000)	1.0	0.5	0.4	0.5	0.4
DR of stage I colorectal cancer (per 1000)	2.5	0.8	0.8	0.7	0.7
DR of stage II colorectal cancer (per 1000)	0.9	0.3	0.3	0.2	0.3
DR of stage III colorectal cancer (per 1000)	0.8	0.3	0.2	0.3	0.2
DR of stage IV colorectal cancer (per 1000)	0.2	0.1	<0.1	<0.1	0.1
Females					
Participation rate, %	52.0	76.7	91.3	93.3	94.3
Proportion of positive FIT results, %	4.6	3.7	3.3	3.4	3.8
Colonoscopic assessment rate, %	82.9	84.8	87.8	88.2	86.8
Successful cecal intubation rate, %	NA	NA	NA	NA	NA
DR of advanced adenoma (per 1000)	11.7	6.4	5.4	5.5	5.7
DR of colorectal cancer (per 1000)	2.4	1.1	1.1	0.8	1.0
DR of advanced neoplasia[a] (per 1000)	14.1	7.5	6.5	6.3	6.7
PPV for adenoma,[b] %	42.8	34.6	33.3	33.4	32.9
PPV for advanced adenoma, %	30.5	20.4	18.5	18.0	17.2
PPV for colorectal cancer, %	6.2	3.4	3.8	2.7	3.1
PPV for advanced neoplasia,[a] %	36.7	23.8	22.3	20.8	20.3
DR of proximal colon cancer (per 1000)	0.6	0.4	0.6	0.4	0.6
DR of distal colon cancer (per 1000)	1.4	0.3	0.3	0.3	0.2
DR of rectal cancer (per 1000)	0.4	0.3	0.2	0.2	0.2
DR of stage I colorectal cancer (per 1000)	1.3	0.5	0.4	0.4	0.5
DR of stage II colorectal cancer (per 1000)	0.4	0.2	0.2	0.2	0.1
DR of stage III colorectal cancer (per 1000)	0.5	0.3	0.3	0.2	0.2
DR of stage IV colorectal cancer (per 1000)	<0.1	<0.1	<0.1	0	<0.1

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005–2016). A compliant participant was defined as one who had 2, 3, 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). The participation rate is per 100 subjects invited. The proportion of positive FIT results is per 100 subjects undergoing FIT screening. The colonoscopic assessment rate is per 100 subjects with positive FIT results. The successful cecal intubation rate, if available, would be per 100 subjects with positive FIT results undergoing colonoscopic assessment. The DRs of advanced adenoma, colorectal cancer, and advanced neoplasia are per 1000 subjects undergoing FIT screening. The PPVs are per 100 subjects with positive FIT results undergoing colonoscopic assessment. Anal cancer cases were excluded from the number of cases by tumor stage.

DR, detection rate; FIT, fecal immunochemical test; NA, not available; PPV, positive predictive value.

[a]Advanced neoplasia indicates advanced adenoma and colorectal cancer.

[b]Also referred to as the adenoma detection rate.

studies by Zorzi et al,[6,7] although they pooled males and females in their study. In their data, the proportion of positive FIT results, the DR of advanced adenoma, and the PPV for advanced neoplasia decreased between the first and the second rounds and then stabilized, whereas the DR of CRC decreased until the third round before plateauing.[6] Our results followed a similar pattern, but all DRs as well as the proportion of positive FIT results continued to decrease until the third round. In addition, this trend was more pronounced for males.

Regarding the trends in the DR by disease site, our findings were practically identical to those reported by Zorzi et al[7] for both sexes combined. The detection of proximal colon cancer decreased between the first and the second rounds and then stabilized, whereas the detection of distal colon cancer decreased over 5 rounds. In addition, the DR of proximal colon cancer remained at a higher level than that of distal colon cancer, especially among females. Many colonoscopy-verified diagnostic studies[12] and studies on the proportional incidence of

Table 5. Compliant Participants: Comparison of the First, Third, Fourth, and Fifth Screening Rounds Vs the Second Round for the Proportion of Positive FIT Results, the Colonoscopic Assessment Rate, the DR of Colorectal Adenoma and Colorectal Cancer, and the PPV for Colorectal Adenoma and Colorectal Cancer, by Sex

	Round					
	1st	2nd	3rd	4th	5th	*P* value[c]
Males						
Proportion of positive FIT results	1.43 (1.39–1.47)	1.00 (ref)	0.79 (0.76–0.82)	0.78 (0.75–0.82)	0.81 (0.78–0.85)	
Colonoscopic assessment rate	0.98 (0.95–1.01)	1.00 (ref)	1.01 (0.97–1.06)	1.03 (0.99–1.08)	1.01 (0.96–1.06)	
DR of advanced adenoma	1.94 (1.84–2.05)	1.00 (ref)	0.72 (0.67–0.78)	0.75 (0.69–0.82)	0.68 (0.62–0.75)	
DR of colorectal cancer	2.85 (2.47–3.28)	1.00 (ref)	0.78 (0.63–0.96)	0.70 (0.55–0.88)	0.71 (0.55–0.91)	
DR of advanced neoplasia[a]	2.04 (1.94–2.15)	1.00 (ref)	0.73 (0.68–0.78)	0.74 (0.69–0.80)	0.68 (0.62–0.74)	
PPV for adenoma[b]	1.15 (1.10–1.19)	1.00 (ref)	0.93 (0.88–0.99)	0.95 (0.89–1.01)	0.91 (0.85–0.97)	
PPV for advanced adenoma	1.38 (1.31–1.45)	1.00 (ref)	0.90 (0.83–0.97)	0.93 (0.85–1.00)	0.83 (0.76–0.91)	
PPV for colorectal cancer	2.01 (1.74–2.31)	1.00 (ref)	0.96 (0.78–1.19)	0.86 (0.68–1.08)	0.86 (0.67–1.11)	
PPV for advanced neoplasia[a]	1.45 (1.38–1.52)	1.00 (ref)	0.91 (0.84–0.97)	0.92 (0.85–0.99)	0.83 (0.76–0.91)	
Females						
Proportion of positive FIT results	1.29 (1.25–1.33)	1.00 (ref)	0.86 (0.83–0.90)	0.86 (0.83–0.90)	0.93 (0.89–0.98)	<.0001
Colonoscopic assessment rate	0.98 (0.95–1.01)	1.00 (ref)	1.03 (0.99–1.08)	1.04 (0.99–1.09)	1.02 (0.97–1.08)	.8776
DR of advanced adenoma	1.89 (1.76–2.03)	1.00 (ref)	0.80 (0.72–0.88)	0.78 (0.70–0.87)	0.79 (0.70–0.89)	.0771
DR of colorectal cancer	2.36 (1.99–2.80)	1.00 (ref)	0.97 (0.77–1.21)	0.68 (0.52–0.89)	0.79 (0.60–1.04)	.0118
DR of advanced neoplasia[a]	1.96 (1.84–2.09)	1.00 (ref)	0.82 (0.75–0.90)	0.77 (0.69–0.85)	0.79 (0.71–0.88)	.0050
PPV for adenoma[b]	1.25 (1.18–1.31)	1.00 (ref)	0.96 (0.89–1.03)	0.95 (0.88–1.03)	0.94 (0.86–1.02)	.0747
PPV for advanced adenoma	1.50 (1.40–1.61)	1.00 (ref)	0.90 (0.81–0.99)	0.87 (0.79–0.97)	0.83 (0.74–0.93)	.0374
PPV for colorectal cancer	1.86 (1.57–2.21)	1.00 (ref)	1.08 (0.86–1.36)	0.76 (0.58–0.99)	0.83 (0.63–1.09)	.5750
PPV for advanced neoplasia[a]	1.55 (1.45–1.66)	1.00 (ref)	0.92 (0.84–1.01)	0.86 (0.77–0.94)	0.83 (0.75–0.92)	.0742

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005–2016). A compliant participant was defined as one who had 2, 3, 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). Numbers are rate ratios from multivariate Poisson regression models. Numbers in parentheses are 95% CIs.
DR, detection rate; FIT, fecal immunochemical test; PPV, positive predictive value.
[a]Advanced neoplasia indicates advanced adenoma and colorectal cancer.
[b]Also referred to as the adenoma detection rate.
[c]Test for interaction between sex and screening round.

interval CRC[13,14] showed a modest difference in the sensitivity of FIT for proximal vs distal lesions.[13] Other investigations, however, have shown a substantially lower sensitivity of FIT for right-sided tumors.[7,15,16]

Previous studies have not evaluated trends in the tumor-stage–specific probability of diagnosis of CRC after the first round. We observed a decrease that was distributed evenly among stage I and stage II CRC. The DR of stage I and stage II CRC stabilized, for both sexes, only at the fourth round.

Overall, the pattern of decrease in all DRs and, in particular, the continuous decrease in the detection of distal colon cancer for 5 rounds confirmed the notion that the diagnoses of advanced adenoma were cumulative over the screening rounds.[7] These data also provided circumstantial evidence that FIT screening prevents the progression of an appreciable subset of advanced adenomas.[3,6,7] Indeed, because the sensitivity of FIT can be assumed to be constant across rounds, the changes in the DRs of CRC and distal colon cancer can be explained only with a decrease in the prevalence of preclinical detectable CRC and distal colon cancer. This, in turn, only can be the result of the detection and treatment of some advanced adenomas next to become invasive diseases. Whether this may translate into a significant reduction in the absolute incidence of CRC compared with a nonscreening situation is a question that warrants further research.[17,18]

Our results have policy implications. First, organized or programmatic cancer screening models have advantages over opportunistic screening practice including, for example, larger coverage and lower risk of overdiagnosis and overtreatment. Our findings indicate that a regular invitation–re-invitation system also would increase the cumulative sensitivity of FIT screening and its effectiveness in preventing distal CRC.

Second, people with compliant participation in 5 screening rounds, necessarily coupled with negative FIT results, should be informed that they have a substantial decrease in the risk of being diagnosed with an advanced lesion. Screening programs aim to maximize their effectiveness by maximizing the uptake. Over the years, however, the imperative to ensure that people invited make an informed choice about participating or not has emerged and now is widely accepted.

Third, our results may be of help in the planning of endoscopy services. Different approaches are being developed to prioritize the access of patients, to create appropriate time slots for them, and to allocate the most experienced endoscopists based on the expected diagnostic yield. The criteria currently used include the indication[19] and other clinical characteristics of

Table 6. Compliant Participants: Comparison of the First, Third, Fourth, and Fifth Screening Rounds Vs the Second Round for the DR of Colorectal Cancer by Disease Site, Tumor Stage, and Sex

	Round				
	1st	2nd	3rd	4th	5th
Males					
DR of proximal colon cancer	2.01 (1.54–2.63)	1.00 (ref)	1.03 (0.73–1.46)	0.91 (0.62–1.34)	1.00 (0.67-1.50)
DR of distal colon cancer	3.80 (3.07–4.70)	1.00 (ref)	0.60 (0.42–0.84)	0.37 (0.24–0.58)	0.43 (0.27–0.69)
DR of rectal cancer	2.32 (1.75–3.07)	1.00 (ref)	0.79 (0.53–1.18)	0.96 (0.64–1.44)	0.74 (0.46–1.20)
DR of stage I colorectal cancer	3.15 (2.57–3.85)	1.00 (ref)	0.86 (0.64–1.15)	0.73 (0.53–1.02)	0.72 (0.51–1.03)
DR of stage II colorectal cancer	2.66 (1.93–3.65)	1.00 (ref)	0.92 (0.59–1.43)	0.54 (0.31–0.94)	0.68 (0.39–1.18)
DR of stage III colorectal cancer	2.51 (1.81–3.46)	1.00 (ref)	0.57 (0.34–0.96)	0.74 (0.44–1.23)	0.55 (0.30–1.02)
DR of stage IV colorectal cancer	3.73 (1.68–8.29)	1.00 (ref)	0.36 (0.07–1.74)	0.45 (0.09–2.19)	0.88 (0.22–3.45)
Females					
DR of proximal colon cancer	1.39 (1.05–1.85)	1.00 (ref)	1.16 (0.83–1.61)	0.76 (0.51–1.13)	1.11 (0.76–1.62)
DR of distal colon cancer	4.37 (3.27–5.84)	1.00 (ref)	0.93 (0.62–1.40)	0.68 (0.42–1.10)	0.46 (0.25–0.85)
DR of rectal cancer	1.57 (1.10–2.24)	1.00 (ref)	0.74 (0.46–1.20)	0.56 (0.32–0.99)	0.66 (0.37–1.18)
DR of stage I colorectal cancer	2.81 (2.20–3.59)	1.00 (ref)	0.84 (0.59–1.18)	0.71 (0.48–1.05)	0.83 (0.56–1.23)
DR of stage II colorectal cancer	2.53 (1.66–3.86)	1.00 (ref)	1.17 (0.68–2.01)	0.88 (0.47–1.63)	0.68 (0.33–1.42)
DR of stage III colorectal cancer	1.54 (1.12–2.12)	1.00 (ref)	0.88 (0.58–1.32)	0.58 (0.35–0.96)	0.60 (0.35–1.03)
DR of stage IV colorectal cancer	4.15 (0.86–19.99)	1.00 (ref)	3.70 (0.80–17.12)	0	0.90 (0.09–9.36)

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005–2016). A compliant participant was defined as one who had 2, 3, 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). Numbers are as relative risk ratios from multinomial logistic regression models. Numbers in parentheses are 95% CIs. Anal cancer cases were excluded from the number of cases by tumor stage.
DR, detection rate.

patients.[20] Our results suggest that compliant long-term participation in FIT screening must be included among the latter.

Fourth, these findings have relevance to the hypothesis of using risk prediction models based on established risk factors for allocation to personalized screening intervals and/or protocols. A systematic review showed that screening history is not among the most commonly used risk factors (age, sex, family history, obesity, and smoking).[21] For subjects allocated to standard FIT screening, however, a compliant participation in 5 to 6 rounds may alter the risk of disease to a substantial extent. We agree with the view that screening history cannot be ignored.[22] The number of previous negative tests, if combined with the amount of hemoglobin in negative FIT, could identify a small group with very high risk and a large population with minimal risk.[23] For example, Zorzi et al[6] proposed increasing the cut-off value for positivity or extending the screening interval for women and younger individuals after 3 negative FITs (provided that the incidence of interval cancer does not exceed the maximum acceptable levels).

This study had some major weaknesses. First, the sharp decrease in the number of subjects undergoing FIT between the first and the fifth round—inherent to the study design—caused an increasing random variation in results. The decrease in the number of compliant participants, however, mainly was owing to external factors (ie, late invitation, screening cessation at age 70 years, migration, and death). These factors accounted, for example, for more than 75% of subjects who participated in the fourth round, but not in the fifth round (data not shown). This suggests that the findings of the last rounds were not affected by major selection biases.

Second, previous studies have shown that the performance measures of follow-up rounds depend on the number of FITs and the chosen cut-off values. With lower cut-off values or with 2 FIT screenings, more advanced neoplasias were detected at the baseline round, and fewer during subsequent rounds.[8] Consequently, our results cannot be generalized to different screening protocols.

Theoretically, studies of this type may be affected by another potential bias that relates to those subjects with positive FIT results and negative colonoscopy who are re-invited to screening some rounds later. These subjects, who are at low risk of disease, might influence the results at subsequent rounds. It must be noted, however, that this cannot be the case for the present study, in which follow-up evaluation ceased on the day of receipt of colonoscopy for a positive FIT result.

In summary, compliant participants had a lower Q20 proportion of positive FIT results than the total screening population. For them, some major performance measures continued to decrease even after the expected decrease between the first and the second rounds. Between the second and the third rounds, the proportion of positive FIT results and the DR of advanced adenoma, CRC, and advanced neoplasia decreased by 20% to 30% among males. For both sexes, the DR of distal colon cancer decreased until the fourth (males) and fifth rounds (females). These findings add circumstantial evidence that FIT screening prevents the progression of an appreciable subset of advanced

adenomas, and have implications for the communication of benefits and harms of the screening process, the planning of endoscopy services, and the development of risk-based screening strategies.

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Conflicts of interest Q9
The authors disclose no conflicts.