Colonoscopy later than 270 days in a fecal immunochemical test-based population screening program is associated with higher prevalence of colorectal cancer

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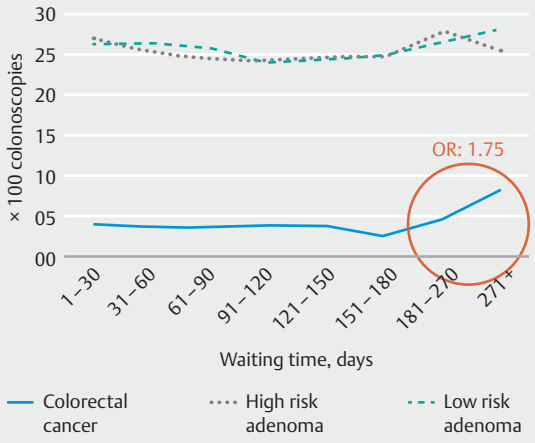
GRAPHICAL ABSTRACT

A time to colonoscopy longer than 270 days in FIT-based population screening program is associated with higher prevalence of colorectal cancer



- In screening programs, a 30-day interval is recommended between positive FIT result and colonoscopy
- More than 50% of post-FIT colonoscopies in the Italian screening program are performed after 30 days
- According to our study, prevalence of CRC increases by nearly 2-fold 270 days after FIT+

ABSTRACT

Background Colorectal cancer (CRC) screening programs based on fecal immunochemical testing (FIT) generate substantial pressure on colonoscopy capacity in Europe. Thus, a relevant proportion of FIT-positive patients undergo colonoscopy after the recommended 30-day interval, which may be associated with an excess CRC risk.

Methods In a cohort of 50–69-year-old patients undergoing biennial rounds of FIT (OC-Hemodia latex agglutination test; cutoff 20 µg hemoglobin/g feces) between 2004 and 2017, we assessed the outcome at colonoscopy (low/high risk adenoma/CRC/advanced stage CRC) among FIT-positive patients, according to different time intervals. The association of each outcome with waiting time, and demographic and clinical factors, was analyzed through multivariable analysis.

Results 123 138/154 213 FIT-positive patients (79.8%) underwent post-FIT colonoscopy. Time to colonoscopy was ≤30 days, 31–180 days, and ≥181 days in 50 406 (40.9%), 71 724 (58.3%), and 1008 (0.8%) patients, respectively. At colonoscopy, CRC, high risk adenoma, and low risk adenoma were diagnosed in 4813 (3.9%), 30 500 (24.8%), and 22 986 (18.7%) patients, respectively. An increased CRC prevalence at colonoscopy was observed for a time to colonoscopy of ≥270 days (odds ratio [OR] 1.75, 95% confidence interval [CI] 1.15–2.67), whereas it was stable for waiting times of <180 days. The proportion of advanced CRC also increased after 270 days (OR 2.79, 95%CI 1.03–7.57). No increase for low or high risk adenomas according to time to colonoscopy was observed.

Conclusion In a European FIT-based screening program, post-FIT colonoscopy after 9 months was associated with an increased risk of CRC and CRC progression.

Introduction

The immunochemical fecal test (FIT) appears to be a more acceptable and accurate alternative to guaiac-based fecal test [1–4]. FIT implementation in organized screening programs has been associated with a substantial reduction in colorectal cancer (CRC) mortality [5]. In addition, a very high cumulative detection of advanced adenomas has been shown after multiple rounds of FIT, indirectly supporting FIT efficacy in CRC incidence prevention [6,7]. Thus, FIT-based screening programs are now being implemented in several European countries, with approximately 4 million tests estimated to be performed each year [8]. As a first-level test, FIT can only filter out a fraction of the asymptomatic population at higher risk of advanced neoplasia. Its ultimate efficacy, however, depends on post-FIT-positive colonoscopy during which early CRC can be diagnosed and precancerous polyps removed.

In recent years, the time interval between a positive FIT test and post-FIT colonoscopy has been shown to affect FIT efficacy. In detail, a ≥ 10-month interval has been associated with a higher prevalence of CRC – especially its advanced stages – and advanced adenomas at post-FIT colonoscopy [9]. This was postulated to be due to the progression of FIT-positive advanced neoplasia during an excessively delayed post-FIT colonoscopy, and such hypothesis has been confirmed in a recent simulation model [10]. Recently, such association has been confirmed in the FIT-based Taiwanese screening program [11], as well as following a positive guaiac-based fecal test in Israel [12]. These data have yet to be confirmed in a European setting, where organizational issues may show different outcomes.

According to European CRC screening guidelines, the interval to post-FIT colonoscopy should be within 31 days [13]. This criterion is actively surveyed in Italy, where a ≥ 90 % interval to post-FIT colonoscopies in ≤ 30 days is recommended as a desirable programmatic outcome [14]. However, due to organizational issues and limited endoscopy capacity, more than half of colonoscopies in Italian organized programs are performed beyond the 30-day cutoff.

The aim of the current study was to assess in an actively monitored FIT-based screening program in Italy whether a delay to post-FIT colonoscopy was associated with a higher risk of CRC.

Methods

Setting

In the Veneto Region (northeastern Italy; population 4 915 000), a population-based screening program for CRC was first implemented in 2002. The screening program involves 50–69-year-old residents who are invited via mail every 2 years to perform a single FIT, without any dietary restriction. Individuals who do not respond to the first invitation are mailed a reminder, usually within 6 months. The OC-Hemodia latex agglutination test, developed with the OC-Sensor Micro instrument (Eiken, Tokyo, Japan), is used. Quantitative hemoglobin analysis is performed with automated instruments. The cutoff for test positivity is 20 µg hemoglobin/g feces (100 ng Hb/mL buffer). Individuals are notified of their results by mail and people with a negative FIT result are advised to repeat the screening 2 years later. Individuals with a positive screening test are contacted by telephone to undergo a colonoscopy performed at an endoscopy referral center during dedicated sessions. After colonoscopy, patients are referred for surgery, postcolonoscopy surveillance, or further rounds of FIT, depending on the outcome of colonoscopy.

All the data collected on each screening round (FIT plus any colonoscopy) are recorded using dedicated software, and are available as individual records.

Dataset

We used the screening database to identify all patients who had a positive FIT result between 1 January 2004 and 4 October 2017. The date of each FIT was recorded, together with the following information: whether the patient underwent colonoscopy, the reasons for noncompliance or for exclusion from colonoscopy, the date of colonoscopy, and the outcome of colonoscopy, classified as CRC, high risk adenoma (patients with at least three adenomas or at least one adenoma ≥ 10 mm or at least one adenoma with villous histology or high grade dysplasia), low risk adenoma (patients with one to two tubular adenomas < 10 mm, with low grade dysplasia), or negative. Up to three lesions (the most severe) were recorded for each colonoscopy. TNM stage of CRC was available for 64.4 % cases.

The interval between the date of FIT testing and the date of colonoscopy was classified into the following categories: 1–30, 31–60, 61–90, 61–120, 121–150, 151–180, 181–270, and > 270 days.

Outcome measures

The following indicators were calculated by time to colonoscopy: 1) percent distribution of colonoscopies; 2) detection of CRC, overall and according to TNM stage (% colonoscopies); 3) detection of high risk and low risk adenoma (% colonoscopies).

Statistical analysis

Descriptive statistics, stratified by waiting time for colonoscopy, were used to summarize the results of the screening program.

A multivariable analysis was run to examine the association of each outcome with sex, age (50–59, 60–69 years), calendar period (2004–2008, 2009–2011, 2012–2014, 2015–2017), FIT round (first, subsequent), and waiting time. For each outcome, we computed the odds ratio (OR), with 95 % Wald confidence intervals (CI), estimated using Logistic regression, taking male sex, 50–59-year-old group, first screening round, and 1–30 days of waiting time as reference, and estimating a linear trend across the four 3-year calendar periods.

All statistical tests were two-sided and statistical significance was set at 0.05. SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for all the statistical analyses.

Results

Study population

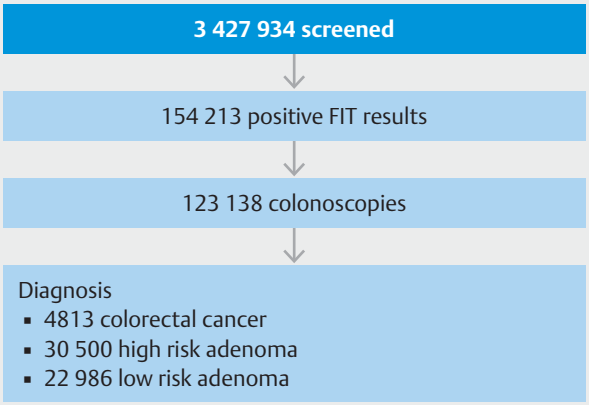
Among the 154 213 FIT-positive individuals during the study period, 123 138 (median age 55 years, interquartile range 50–65 years; male 56.8 %) accepted the invitation to undergo post-FIT colonoscopy (79.8 %) (▶ **Fig. 1**). Of these, 24 463 (19.9 %) had a positive result at the first round of FIT, whereas the remaining individuals were positive at subsequent rounds. The waiting time for colonoscopy was ≤ 30 days in 50 406 cases (40.9 %), 31–180 days in 71 724 cases (58.3 %), and ≥ 181 days in 1008 cases (0.8 %). Detailed distribution according to the 30-day intervals of waiting times is provided in ▶ **Table 1**, as well as temporal distribution of colonoscopies according to annual period. Time to colonoscopy was significantly associated with sex, age, calendar period, and FIT round.

Detection according to waiting times

At colonoscopy, 4813 (3.9 %), 30 500 (24.8 %), and 22 986 (18.7 %) patients presented with a diagnosis of CRC, high risk adenoma, and low risk adenoma, respectively (▶ **Table 1**). As shown in ▶ **Fig. 2**, the detection rate for invasive CRC was stable for waiting times < 180 days, whereas a statistically significant excess was observed after the 270-day cutoff (OR 1.75, 95 %CI 1.15–2.67). Older age, male sex, first vs. subsequent rounds, and early period were also associated with an increased risk of CRC detection (▶ **Table 2**).

Stage at diagnosis was available for 3121 invasive cancers (64.8 %). Considering only CRCs with stage available, almost half of cases were stage I (48.6 %) and a further 34.5 % were stage II. The proportion of cases at advanced stage (III–IV) increased for patients waiting > 270 days compared with those waiting < 30 days (OR 2.79, 95 %CI 1.03–7.57) (▶ **Table 3**).

No increase in detection rates of low or high risk adenomas according to the duration of the waiting time was observed (▶ **Table 2**).



▶ **Fig. 1** Patients included in the study. FIT, fecal immunochemical test.

Discussion

In an organized screening program, a time to colonoscopy longer than 9 months after a positive FIT result was associated with nearly a 2-fold increase in the detection of invasive CRC and approximately 3-fold increase in the rate of advanced disease. However, we did not find any increase in prevalence of CRC or CRC stage progression within 6 months after a positive FIT test, which supports the overall safety of the 30-day maximum recommended by the European CRC screening guidelines. In the case of a lack of resources, our data also suggest that the 30-day cutoff may be safely extended to at least 60 days, as adopted in other health settings [13].

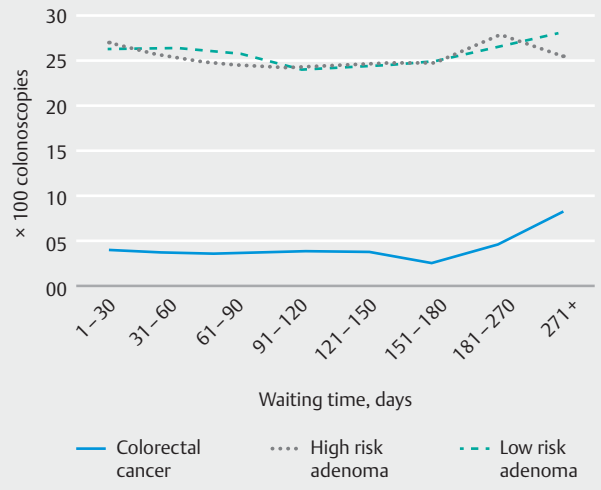
Our data are relevant for the following reasons. First, in a long-lasting FIT program, based on 2-year FIT repetition, less than 50 % of patients underwent colonoscopy within the recommended 30-day period. This may be due to limited endoscopy capacity related to competing indications, such as post-polypectomy surveillance. However, the delay to colonoscopy for FIT-positive patients was minor in most of the cases, as only 0.8 % of the FIT population underwent a colonoscopy after 6 months in our series. When considering that the additional risk due to prolonged waiting times appears only after 9 months, the possible contribution of excessive time to colonoscopy to the overall burden of interval CRC is likely to be small. Such evidence reinforces the relevance of a robust organization when delivering post-FIT colonoscopies. This may explain the nearly 8-fold difference between the 0.8 % of the FIT population undergoing a colonoscopy after 6 months in our study and the 6.3 % in a US-based study [9], where FIT was performed annually, as well as a more than 20-fold difference between the two series after the 9-month cutoff [9].

Second, we confirmed, in a European setting, the prolonged delay needed to generate an excessive risk of CRC and the magnitude of such a risk observed in American and Asian settings [9, 11]. The 9-month interval shown to be significant in our series is, overall, similar to the 7–12-month interval shown in the US-based series [9], and to the ≥ 6 months shown in the Asian series [11]. The 2–3-fold increase in the additional risk of CRC and CRC progression observed in our series is also similar to that observed in the US series, which ranged between 1.37 and 2.25 at different waiting times [9]. Overall, the fact that a prolonged interval is required to induce excessive risk, which is limited in its magnitude, should not be surprising. Although the FIT-positive population is enriched with high risk or advanced adenomas, the actual annual transition rate to CRC has been estimated to be between 2 % and 5 % according to age and sex [15]. Thus, only a minority of advanced lesions will turn into invasive cancer within 1 year from a positive FIT result, supporting the limited magnitude of the risk we observed. For similar reasons, and also considering the much longer sojourn time of a low risk adenoma, it is not surprising that we failed to observe a significant increase in the prevalence of high risk adenomas according to longer time to colonoscopy. However, the approximately 3-fold increase in the risk of advanced CRC after 9 months may be related to the much faster progression across different stages of malignant disease compared with that from a benign to invasive disease.

▶ **Table 1** Main characteristics of the study patients, by waiting time for colonoscopy.

Patients, n (%)[1]	Waiting time for colonoscopy, days									
	1–30	31–60	61–90	91–120	121–150	151–180	181–270	>270	Total	*P* value
Total (row %)	50406 (40.9)	48081 (39.0)	16911 (13.7)	4638 (3.8)	1526 (1.2)	568 (0.5)	701 (0.6)	307 (0.2)	123138 (100)	–
Sex										
▪ Men	28355 (56.3)	27347 (56.9)	9784 (57.9)	2676 (57.7)	861 (56.4)	324 (57.0)	410 (58.5)	193 (62.9)	69950 (56.8)	0.004
▪ Women	22048 (43.7)	20729 (43.1)	7127 (42.1)	1962 (42.3)	665 (43.6)	244 (43.0)	291 (41.5)	114 (37.1)	53180 (43.2)	
Age, years										
▪ 50–59	23065 (45.8)	22630 (47.1)	8213 (48.6)	2216 (47.8)	728 (47.7)	302 (53.2)	288 (41.1)	131 (42.7)	57573 (46.8)	<0.001
▪ 60–69	27341 (54.2)	25451 (52.9)	8698 (51.4)	2422 (52.2)	798 (52.3)	266 (46.8)	413 (58.9)	176 (57.3)	65565 (53.2)	
Period										
▪ 2004–2008	10871 (21.6)	8501 (17.7)	3002 (17.8)	848 (18.3)	334 (21.9)	103 (18.1)	128 (18.3)	89 (29.0)	23876 (19.4)	<0.001
▪ 2009–2011	14767 (29.3)	9815 (20.4)	2916 (17.2)	884 (19.1)	420 (27.5)	145 (25.5)	234 (33.4)	79 (25.7)	29260 (23.8)	
▪ 2012–2014	13938 (27.7)	14567 (30.3)	4695 (27.8)	986 (21.3)	272 (17.8)	110 (19.4)	167 (23.8)	69 (22.5)	34804 (28.3)	
▪ 2015–2017	10830 (21.5)	15198 (31.6)	6298 (37.2)	1920 (41.4)	500 (32.8)	210 (37.0)	172 (24.5)	70 (22.8)	35198 (28.6)	
FIT round										
▪ First	9067 (18.0)	9465 (19.7)	4023 (23.8)	1105 (23.8)	260 (17.0)	150 (26.4)	271 (38.7)	122 (39.7)	24463 (19.9)	<0.001
▪ Subsequent	41339 (82.0)	38616 (80.3)	12888 (76.2)	3533 (76.2)	1266 (83.0)	418 (73.6)	430 (61.3)	185 (60.3)	98675 (80.1)	
Diagnosis										
▪ CRC	2085 (4.1)	1811 (3.8)	609 (3.6)	181 (3.9)	58 (3.8)	15 (2.6)	30 (4.3)	24 (7.8)	4813 (3.9)	<0.001
▪ High risk adenoma	13014 (25.8)	11668 (24.3)	3984 (23.6)	1075 (23.2)	361 (23.7)	137 (24.1)	188 (26.8)	73 (23.8)	30500 (24.8)	
▪ Low risk adenoma	9306 (18.5)	9140 (19.0)	3171 (18.8)	810 (17.5)	269 (17.6)	104 (18.3)	127 (18.1)	59 (19.2)	22986 (18.7)	
▪ Negative	26001 (51.6)	25462 (53.0)	9147 (54.1)	2572 (55.5)	838 (54.9)	312 (54.9)	356 (50.8)	151 (49.2)	64839 (52.7)	
Stage at diagnosis (% of CRC cases)										
▪ I	772 (37.0)	510 (28.2)	156 (25.6)	45 (24.9)	15 (25.9)	7 (46.7)	6 (20.0)	7 (29.2)	1518 (31.5)	0.001
▪ II	492 (23.6)	407 (22.5)	120 (19.7)	29 (16.0)	11 (19.0)	4 (26.7)	9 (30.0)	6 (25.0)	1078 (22.4)	
▪ III	150 (7.2)	176 (9.7)	53 (8.7)	11 (6.1)	2 (3.4)	1 (6.7)	7 (23.3)	4 (16.7)	404 (8.4)	
▪ IV	60 (2.9)	38 (2.1)	17 (2.8)	3 (1.7)	0 (0.0)	2 (13.3)	1 (3.3)	0 (0.0)	121 (2.5)	
▪ Missing	611 (29.3)	680 (37.5)	263 (43.2)	93 (51.4)	30 (51.7)	1 (6.7)	7 (23.3)	7 (29.2)	1692 (35.2)	

FIT, fecal immunochemical test; CRC, colorectal cancer.
[1] % are column % except where stated.



▶ **Fig. 2** Detection of colorectal cancer, high risk adenoma, and low risk adenoma, according to the waiting time for colonoscopy after a positive fecal immunochemical test result.

There are limitations to our study. First, we could not speculate on the causal relationship between the time to colonoscopy and the progression of disease. Some well-known characteristics associated with higher prevalence of CRC, such as male sex, older age, and first FIT test were also significantly associated with increasing time to colonoscopy. But it is also possible that residual confounding factors may partly explain the observed results. In detail, patient-related bias (i. e. unhealthy lifestyle or fear of colonoscopy) could also explain an independent increased risk of CRC and a longer time to colonoscopy. However, it is also true that the opposite is much more likely to happen, as CRC patients tend to anticipate the post-FIT colonoscopy as they may see visible bleeding when the CRC is symptomatic.

A minority of patients underwent colonoscopy after > 180 or > 270 days. Reasons for such prolonged delay are not related to organizational issues, but we do not have information to exclude the possibility that these patients decided to undergo colonoscopy because some gastrointestinal symptoms occurred. This could partly explain the higher incidence of cancer, and of cancers at advanced stages at diagnosis, in these subgroups.

Second, the stage at diagnosis of CRC could not be retrieved for about one-third of cases. Although missing data are plausibly random, this could limit the reliability of our results. However, our findings are in line with those shown in the US series, mitigating the risk of bias [9]. Finally, our results may vary according to different FIT cutoffs used. Data on the whole population are not available, but subanalysis on the cohort for which hemoglobin level was present did not show any significant differences (data not shown).

In a FIT-based organized program in a European setting, we showed an additional risk of CRC and CRC progression in a minority of patients undergoing post-FIT colonoscopy after 9 months. This supports the current European recommendation

▶ **Table 2** Multivariate analysis according to the type of lesion detected.

	Odds ratio	95 %CI	*P* value
Colorectal cancer			
Waiting time, day			
▪ 31–60	0.97	0.91–1.04	0.40
▪ 61–90	0.94	0.86–1.03	0.19
▪ 91–120	1.03	0.88–1.20	0.75
▪ 121–150	0.96	0.73–1.25	0.75
▪ 151–180	0.67	0.40–1.12	0.12
▪ 181–270	0.96	0.66–1.39	0.83
▪ >270	1.75	1.15–2.67	0.01
Age, 60–69 years	1.39	1.31–1.48	<0.001
Sex, female	0.84	0.79–0.89	<0.001
FIT round, subsequent	0.74	0.69–0.79	<0.001
Calendar year, linear trend	0.75	0.73–0.77	<0.001
High risk adenoma			
Waiting time, days			
▪ 31–60	0.90	0.88–0.93	<0.001
▪ 61–90	0.85	0.81–0.88	<0.001
▪ 91–120	0.83	0.77–0.89	<0.001
▪ 121–150	0.89	0.79–1.01	0.06
▪ 151–180	0.88	0.72–1.07	0.19
▪ 181–270	0.94	0.80–1.12	0.50
▪ >270	0.79	0.60–1.03	0.08
Age, 60–69 years	1.17	1.14–1.20	<0.001
Sex, female	0.59	0.58–0.61	<0.001
FIT round, subsequent	0.66	0.64–0.68	<0.001
Calendar year, linear trend	1.04	1.02–1.05	<0.001
Low risk adenoma			
Waiting time, days			
▪ 31–60	1.02	0.99–1.06	0.15
▪ 61–90	1.00	0.96–1.05	0.97
▪ 91–120	0.92	0.85–0.99	0.03
▪ 121–150	0.94	0.82–1.08	0.39
▪ 151–180	0.99	0.80–1.22	0.90
▪ 181–270	0.95	0.78–1.15	0.61
▪ >270	1.02	0.77–1.36	0.89
Age, 60–69 years	1.22	1.18–1.25	<0.001
Sex, female	0.75	0.72–0.77	<0.001
FIT round, subsequent	0.96	0.93–1.00	0.03
Calendar year, linear trend	1.05	1.04–1.06	<0.001

CI, confidence interval; FIT, fecal immunochemical test.

▶ **Table 3** Multivariate analysis according to the stage of colorectal cancer detected.

	Odds ratio	95 %CI	*P* value
Stage I			
Waiting time, days			
▪ 31–60	0.76	0.68–0.86	<0.001
▪ 61–90	0.68	0.57–0.81	<0.001
▪ 91–120	0.72	0.53–0.97	0.03
▪ 121–150	0.67	0.40–1.13	0.13
▪ 151–180	0.87	0.41–1.83	0.71
▪ 181–270	0.53	0.24–1.18	0.12
▪ >270	1.37	0.65–2.92	0.41
Age, 60–69 years	1.42	1.27–1.57	<0.001
Sex, female	0.83	0.75–0.92	0.001
FIT round, subsequent	0.79	0.70–0.89	<0.001
Calendar year, linear trend	0.64	0.61–0.68	<0.001
Stage II			
Waiting time, days			
▪ 31–60	0.96	0.84–1.09	0.53
▪ 61–90	0.82	0.67–1.00	0.05
▪ 91–120	0.72	0.50–1.05	0.09
▪ 121–150	0.78	0.43–1.43	0.43
▪ 151–180	0.77	0.29–2.06	0.60
▪ 181–270	1.20	0.62–2.34	0.59
▪ >270	1.77	0.78–4.00	0.19
Age, 60–69 years	1.37	1.21–1.55	<0.001
Sex, female	0.91	0.81–1.03	0.15
FIT round, subsequent	0.69	0.60–0.79	<0.001
Calendar year, linear trend	0.63	0.59–0.67	<0.001
Stages III–IV			
Waiting time, days			
▪ 31–60	1.04	0.86–1.27	0.66
▪ 61–90	0.94	0.72–1.24	0.67
▪ 91–120	0.69	0.40–1.19	0.18
▪ 121–150	0.31	0.08–1.27	0.10
▪ 151–180	1.20	0.38–3.78	0.75
▪ 181–270	2.35	1.15–4.80	0.02
▪ >270	2.79	1.03–7.57	0.04
Age, 60–69 years	1.46	1.22–1.74	<0.001
Sex, female	0.83	0.70–0.99	0.04
FIT round, subsequent	0.58	0.47–0.71	<0.001
Calendar year, linear trend	1.05	0.97–1.14	0.27

CI, confidence interval; FIT, fecal immunochemical test.

of limiting the duration of time to colonoscopy to 30 days, although a 60-day interval would also appear reasonably safe.

Competing interests

The authors declare that they have no conflicts of interest.

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