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Using fecal immunochemical test values below conventional cut-off to individualize colorectal cancer screening

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ABSTRACT

Background and study aims Of the participants in the Danish screening program, 89.9 % to 92.5 % have fecal immunochemical test (FIT) values < 10 µg/g feces (equivalent to 50 ng hemoglobin/mL buffer). This study aimed to investigate the risk of interval colorectal cancer (CRC) in this group before the next biennial screening round.

Patients and methods This cohort study included all citizens from the region of Southern Denmark who participated in the Danish bowel screening program from 2014 trough 2016 and had a FIT value < 10 µg/g feces. Individuals receiving a CRC diagnosis were identified through the national CRC registry, with a follow up of 2 years corresponding to the current screening interval. We also examined the 3-year CRC incidence. Hazard ratios (HRs) were estimated using univariate and multivariate Cox proportional hazard regression models.

Results Data from 185,654 citizens presenting with a FIT value < 10 µg/g feces were eligible for analysis. Overall, interval CRC incidence was 0.07 % within 2 years with HRs of 4.16 (95 % confidence interval [CI] 2.67;6.48) and 5.8 (95 % CI 3.34;10.05) for FIT values of 4 to 6.9 µg/g feces and 7 to 9.9 µg/g feces, respectively, compared to those having a FIT value below the limit of quantification of 4 µg/g feces. After 3 years, the overall CRC incidence increased to 0.14 %; however, this was not significant.

Conclusions This study demonstrates a positive correlation between FIT value and risk of interval cancer even for very low values. It further suggests that an increase in the screening interval could be reasonable in the low FIT categories.

Introduction

The Danish screening program for colorectal cancer (CRC) was launched in March of 2014. Citizens aged 50 to 74 are invited to submit a single stool sample to be analyzed for occult blood using the fecal immunochemical test (FIT, OC sensor, Eiken Chemical, Tokyo, Japan). The first screening round was implemented over 4 years, but since 2018, citizens have been invited biennially. A FIT value ≥ 20 µg/g feces (equivalent to 100 ng hemoglobin/mL buffer) is considered positive, and citizens with a positive FIT test are offered a colonoscopy. If the FIT is negative, a citizen is invited to repeat the stool sample 2 years later [1].

Because the screening program is still rather new, studies to evaluate it are important to be able to optimize the program,

enabling a more focused and individualized approach. By identifying risk groups in the screening population, it is possible to focus the attention on those who are at greater risk. One aspect that could potentially be improved is the screening interval for those who have a negative FIT. Currently, the 2-year interval in Denmark is based on two studies on guaiac fecal occult blood testing from 1996 and a cost-efficiency analysis [1–4].

Of those participating in the Danish screening program, 93 % to 94.8 % present FIT values below the positive threshold and 89.9 % to 92.5 % < 10 µg/g feces (equivalent to 50 ng hemoglobin/mL buffer) [5–7]. This group makes up the vast majority of the screened population; however, exact FIT values in these low categories are not reported in the screening database, hence the risk of CRC in this subpopulation has not been investigated until now.

This study aimed to estimate the incidence of interval colorectal cancer in individuals having a FIT value < 10 µg/g feces in the Danish screening program between two screening rounds, and to stratify this risk into FIT categories using the exact FIT values in this population. We hypothesized that the incidence of interval CRC is proportional to increments in FIT value. The cancer incidence after 3 years was also examined to investigate what a 1-year increase of the screening interval would imply for this group.

Material and methods

Ethics

This study was approved by the Danish Patient Safety Authority (ref. no. 31-1521-150) and the Regional data protection agency (ref. 20–3609).

Study population

The study population consisted of all citizens who submitted a fecal sample from March 2014 through December 2016 in the region of Southern Denmark with a FIT value below 10 µg/g feces.

Outcomes

The primary outcome was to investigate the risk of interval colorectal cancer within 2 years of a FIT because this is the current screening interval in Denmark.

We also investigated the risk of colorectal cancer within 3 years of a FIT test to suggest what a 1-year increase in the screening program could mean for the risk of the invited individuals. The 4-year implementation of the first screening round gave us the unique opportunity to examine the 3-year incidence for those screened in 2014 and 2015, to investigate the possible effect of increasing the screening interval with 1 year.

Methods

The exact FIT values and dates of sample analysis for every individual were obtained through the Department of Biochemistry and Immunology, Lillebaelt Hospital, Vejle, where all screening stool samples from the region are analyzed.

Through the Danish Colorectal Cancer Group (DCCG) registry, we identified individuals diagnosed with CRC in the region of Southern Denmark from January 2014 until December 2018, as the database has not been updated since. DCCG consists of data from The Danish Cancer Registry, the National Patient Registry, The Central Civil Registration Registry, and The Danish Pathology Registry (from 2016). More than 95 % of colorectal cancers are registered in DCCG [8]. We also obtained time of death and emigration from the Danish Quality Database for Colon Cancer Screening. This database consists of data from the National Patient Registry, the National Pathology Registry, and the Invitation and Administration Module for the national screening as well as the Danish Civil Registration system.

By combining these databases by social security numbers, we did a cohort study to locate individuals being diagnosed with CRC after their screening sample had been analyzed and showed a FIT value < 10 µg/g feces. The follow-up time for each individual was limited to 2 years, corresponding to the screening interval in Denmark, or until date of CRC diagnosis, death or emigration, whichever came first.

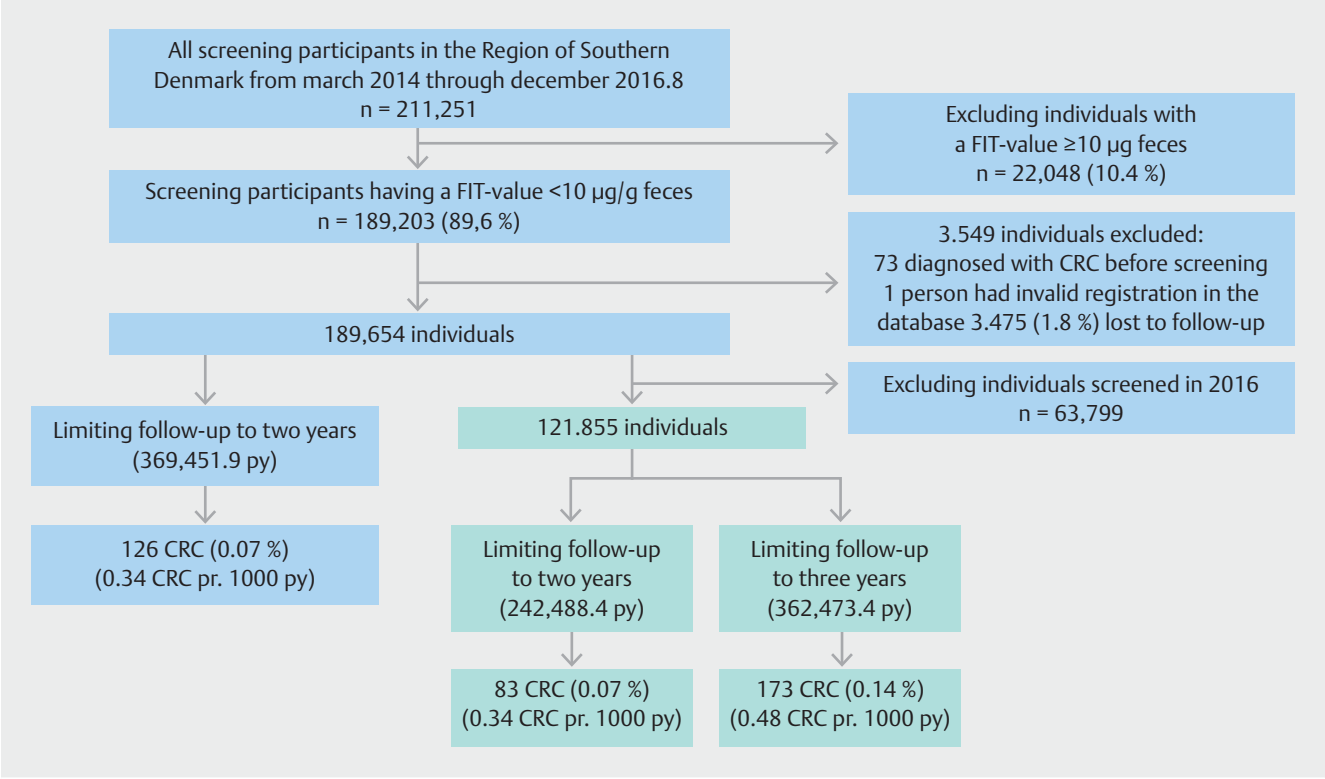
Individuals who had a CRC diagnosis prior to their sample being analyzed were excluded, as they are not part of the ordinary screening program and are asked not to submit a stool sample.

We excluded individuals screened in 2016 from the 3-year incidence analysis, as the second screening round started in 2018 and this could interfere with the results.

Fecal immunochemical test

The participants collected their stool samples using the OC-Auto Sampling bottle 3 (Eiken, Japan). All FIT tests were performed at the Department of Biochemistry and Immunology, Lillebaelt Hospital, Vejle, being accredited by Danish Accreditation Fund (DANAK) according to the ISO 15189:2012 standard that specifies requirements for quality and competence in medical laboratories. The concentration of hemoglobin in the stool sample was quantified by optical measurement of latex agglutination using latex particles coated with anti-human hemoglobin A0 polyclonal antibodies (OC Sensor Eiken, Japan) on OC-Diana instruments (Eiken, Japan).

In the daily routine, the analytical CV were calculated from runs across multiple days using commercially available control material. The following results were obtained: 3 %, 4 % and 3 % at level 13 µg/g feces, 22.5 µg/g feces and 29 µg/g feces, respectively. Analytical CV for FIT concentrations below 10 µg/g feces was determined by dilution of the HK18 control sample (22.5 µg/g feces) to five levels in the 0 to 11 µg/g feces range in phosphate-buffered saline buffer. Each of these five dilutions was aliquoted and stored at –20 C. Each control level was measured on two OC Sensor Pledia instruments (Eiken, Japan) daily in June and July 2020 (77–80 times each) to determine the difference in the daily measurements that reflects the technical accuracy. The coefficients of variation were determined as 36.4 % (1.9 µg/g feces), 23.9 % (3.6 µg/g feces), 22.3 % (4.3 µg/g feces), 14.0 % (6.6 µg/g feces), and 9.8 % (9.1 µg/g feces). The limit of quantification in this study was set to 4 µg/g feces (equivalent to 20 ng/mL buffer), based on an acceptance criterion of 20 %.



▶ **Fig. 1** Flowchart of the study population. FIT, fecal immunochemical test; CRC, colorectal cancer; py, person-years. Blue boxes represent the 3-year analysis.

Statistical analysis

CRC incidence was determined per patient but also reported as incidence rate per 1000 person-years (py). Baseline characteristics were compared using X^2-test for variables with no cell values below five and Fisher's Exact test for variables with cell values below five to determine if the CRC proportions were statistically differently distributed in the subgroups. Hazard ratios (HRs) were calculated using Cox proportional hazards regressions. Cox proportional hazards regressions were also performed in the subgroup with 3 years of follow-up to test if the HR for CRC incidence rose significantly for each FIT group by increasing the screening interval by 1 year. Schönfeld residuals were examined to verify the proportional hazard assumption. Significance level was set at 5 % and 95 % confidence intervals (CIs) were calculated. The FIT category was tested for interaction with the remaining variables (age, sex, year screened). Covariates of age and sex were also tested for interaction. Cumulative CRC incidence proportion curves were created stratified by FIT category. CIs (95 %) for CRC incidence rate were estimated using the exact test for a Poisson distribution. Data management and statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc. SAS 9.4. Cary, North Carolina, United States) and RStudio statistical software package, Version 1.2.5019 (R Development Core Team, Boston, Massachusetts, United States).

Results

From March 2014 through December 2016, 211,251 individuals participated in the screening program in the Region of Southern Denmark. Of these, 189,203 individuals (89.6 %) had a FIT value < 10 µg/g feces. Of these, 3,549 people were excluded: 3,475 (1.8 %) were lost to follow-up, 73 had a diagnosis of CRC before the sample was analyzed, and one individual had invalid registrations in the databases.

After exclusions, 185,654 individuals were eligible for analysis. ▶ **Fig. 1** shows a flowchart of the study population.

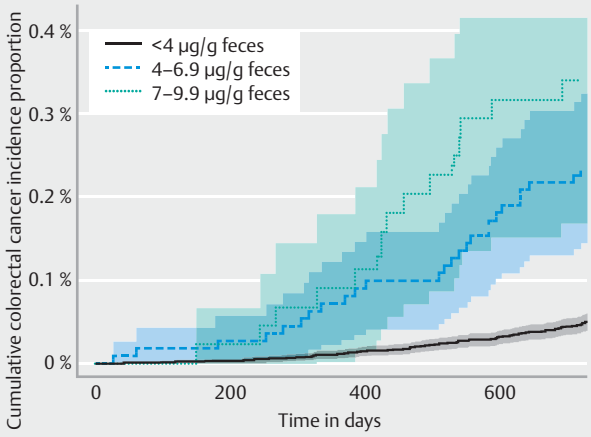
When limiting the follow-up to 2 years for each individual, 126 individuals with interval colorectal cancers were identified. The overall 2-year incidence of interval CRC in the study group was 0.07 % with variations from 0.05 % in those having a FIT value below the quantification limit of 4 µg/g feces to 0.34 % in the group having a FIT value of 7 to 9.9 µg/g feces. FIT values, sex, age groups, and year screened are listed in ▶ **Table 1**. There was no statistically significant difference in interval CRC rates by sex or year screened; however, the CRC rates were significantly different in the age groups as well as the FIT categories, as expected. There were no interactions for FIT categories with age, sex or year screened, as well as no interaction between age and sex. ▶ **Fig. 2** is a visual representation of the cumulative CRC incidence.

Multivariate Cox proportional hazards regression for interval CRC showed HRs of 4.16 (95 % CI 2.67;6.48) and 5.8 (95 % CI 3.34;10.05) for FIT values of 4–6.9 µg/g feces and 7–9.9 µg/g

▶ **Table 1** Characteristics of the screening population with a FIT value < 10 µg/g feces with incidence rate of interval CRC within the next screening round.

	Individuals (%) (n = 185,654)	CRC (%) (n = 126)	*P* value
FIT value (µg/g feces)			
▪ <4	170,195 (91.7)	85 (0.05)	
▪ 4–6.9	11,049 (6.0)	26 (0.24)	
▪ 7–9.9	4,410 (2.4)	15 (0.34)	<0.001[1]
Age (years)			
▪ 49–53	45,067 (24.3)	4 (0.01)	
▪ 54–58	32,294 (17.4)	11 (0.03)	
▪ 59–63	31,773 (17.1)	14 (0.04)	
▪ 64–68	32,020 (17.3)	32 (0.1)	
▪ ≥69	44,500 (24.0)	65 (0.15)	<0.001[1,2]
Sex			
▪ Female	100,704 (54.2)	64 (0.06)	
▪ Male	84,950 (45.7)	62 (0.07)	0.492
Year screened			
▪ 2014	51,258 (27.6)	28 (0.05)	
▪ 2015	70,597 (38.0)	55 (0.08)	
▪ 2016	63,799 (34.4)	43 (0.07)	0.305

FIT, fecal immunochemical test; CRC, colorectal cancer.
[1] Significant at a 5 % level.
[2] Fishers Exact test.



▶ **Fig. 2** Cumulative incidence proportion with 95 % confidence intervals of interval cancers in individuals having a FIT value < 10 µg/g feces within the next screening round.

feces, respectively, compared to those having a FIT value below the quantification limit. There was no statistically significant difference in HRs for sex or year screened. HRs were significantly higher than the reference age group of 49 to 53 years. The HRs with CIs and forest plots are shown in ▶ **Fig. 3**.

When examining the results in CRC pr. 1000 py, the overall incidence rate was 0.34, with variations from 0.25 CRC pr. 1000 py in those having a FIT value below the quantification limit of 4 µg/g feces to 1.72 CRC pr. 1000 py in the group having a FIT value of 7 to 9.9 µg/g feces. ▶ **Table 2** shows the rate of CRC pr. 1000 py.

Three-year results

When excluding the individuals screened in 2016, 121,855 individuals were eligible for analysis, as they had 3 years of follow-up before the second screening round.

A total of 83 individuals with interval CRC within 2 years were identified in this subpopulation corresponding to 0.07 % of the study subpopulation. When extending this follow-up interval to 3 years, 173 cancers were located, corresponding to 0.14 % of the study subpopulation. The CRC incidence distributed by FIT category is listed in ▶ **Table 3**. The subgroup Cox proportional hazard regression models including individuals invited in 2014 and 2015 showed no statistically significant increase in HR between 2 and 3 years of follow-up with HRs of 4.62 (95 % CI 2.64;8.07) vs 3.92 (95 % CI 1.97; 4.63) in the group from 4 to 6.9 µg/g feces and HRs of 6.97 (95 % CI 3.64; 13.33) vs 3.45 (95 % CI 1.95; 6.10).

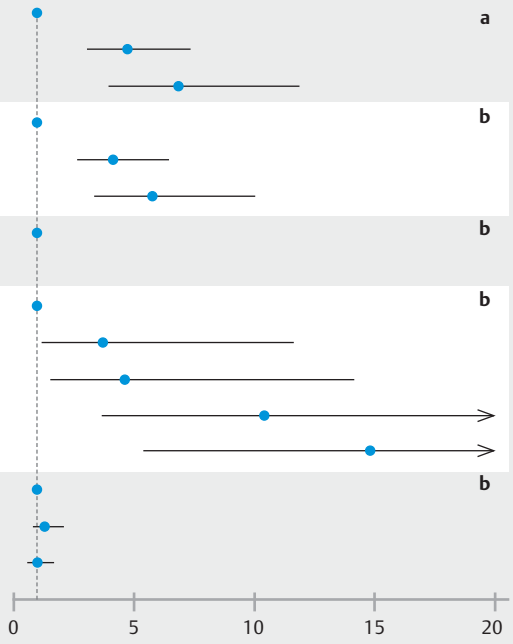
When examining the results in CRC pr. 1000 py, the overall incidence rate was 0.34 CRC pr. 1000 py. When extending the follow-up to 3 years, the incidence increased to 0.48 CRC pr. 1000 py. The results in CRC pr. 1000 py also are listed in ▶ **Table 3**.

Discussion

In this study, we found the overall incidence of CRC within a 2-year screening interval to be 0.07 % at a FIT value < 10 µg/g feces with variations from 0.05 % in the group below the limit of quantification set to 4 µg/g feces to 0.34 % in the group with FIT values of 7 to 9.9 µg/g feces. This study also found a trend of increasing HRs of interval CRC diagnosis with increased FIT values, and individuals with a FIT value between 7 and 9.9 µg/g feces have a 5.8-times higher risk of receiving a CRC diagnosis within 2 years of FIT analysis compared to those having a FIT value < 4 µg/g feces. A similar study found incidences and HRs akin to this study, although their HRs were lower, as they excluded the individuals with FIT values of 0 from the analysis [9]. Previous studies have shown that this trend persists in FIT values > 10 µg/g feces [9–12].

Because implementation of the screening program took 4 years in Denmark, it offered the opportunity to evaluate the incidence of CRC in a 3-year interval in the study population. When extending the follow-up from 2 to 3 years, 90 additional interval cancers were detected, corresponding to a doubling in overall incidence to 0.14 %. However, when examining the HRs after 2 and 3 years of follow-up, we found no statistically significant difference. Meanwhile, the overall incidence of CRC in those declining screening in Denmark is estimated at 0.13 % to

Variable	Level	HR	95% CI	*P* value	
Fecal immunochemical test value	<4 µg/g feces	Ref			a
	4–6.9 µg/g feces	4.74	[3.06; 7.36]	<0.001	
	7–9.9 µg/g feces	6.87	[3.97; 11.89]	<0.001	
Fecal immunochemical test value	<4 µg/g feces	Ref			b
	4–6.9 µg/g feces	4.16	[2.67; 6.48]	<0.001	
	7–9.9 µg/g feces	5.80	[3.34; 10.05]	<0.001	
Sex	Female	Ref			b
	Male	1.09	[0.77; 1.54]	0.632	
Age group	49–53 years	Ref			b
	54–58 years	3.71	[1.18: 11.66]	0.025	
	59–63 years	4.65	[1.53; 14.13]	0.007	
	64–68 years	10.40	[3.67; 29.42]	<0.001	
	69+ years	14.81	[5.39; 40.70]	<0.001	
Year of screening	2014	Ref			b
	2015	1.31	[0.38; 2.07]	0.248	
	2016	1.02	[0.63; 1.64]	0.951	



▶ **Fig. 3** Forest plot with 95% confidence intervals of interval CRC in screening individuals having a FIT value < 10 µg/g feces within the next screening round. Multivariate analysis was adjusted for FIT value, age, sex and year screened. **a** univariate analysis, **b** multivariate analysis. HR, hazard ratio; ref, reference; CI, confidence interval.

▶ **Table 2** CRC pr. 1000 person-years in individuals screened from 2014 to 2016 with a FIT value < 10 µg/g feces stratified by FIT category.

FIT (µg/g feces)	CRC	Py	CRC pr. 1000 py (95% CI)
<4	85	338,831.5	0.25 (0.20;0.31)
4–6.9	26	21,889.2	1.19 (0.78;1.74)
7–9.9	15	8,731.2	1.72 (0.96;2.83)
Total	126	369,451.9	0.34 (0.28–0.41)

CRC, colorectal cancer; FIT, fecal immunochemical test; py; person-years; CI, confidence interval.

0.17% in a 2-year screening round [4, 13]. This prompts a discussion about what is an acceptable risk in a screened population, especially because a new study found that the overall CRC incidence decreases with subsequent screening rounds [14].

A recent Danish study found that raising the FIT-positive threshold to 25 µg/g feces (equivalent to 125 ng hemoglobin/m: buffer) was the optimal cut-off, with a goal of detecting one cancer in 16 colonoscopies [15]. This is one way of optimizing the screening program and using resources effectively. Our study suggests that extending the screening interval in the low FIT groups might also be sensible and safe.

Individuals with a FIT value < 4 µg/g feces made up around 80% of all those screened from 2014 to 2017 in the Region of Southern Denmark, and this group was found to have an overall CRC incidence of 0.05%. In the future, more sensitive methods might be able to lower the limit of quantification, and thus, to further discriminate between individuals with low FIT values and to examine the risk of CRC in these subgroups.

Unexpectedly, we found no statistically significant difference in CRC incidence between men and women. Numerous studies have suggested that the FIT is more sensitive in men than in women, as women more often have right-sided cancer, which tends to bleed less [16–18]. Therefore, we would have expected the number of cancers in the FIT-negative group to be higher in women than in men.

A few limitations were present in this study. If a patient was diagnosed with CRC before 2014 and participated in the screening (even though advised not to), we would not be able to exclude them. Because their CRC risk is higher than the average citizen, this could have falsely increased the CRC incidence in this study. Of the population, 3.475 (1.8%) were lost to follow-up. The most likely explanation for this is that these individuals moved to a different region in Denmark, as we did not obtain CRC diagnoses nor mortality status from outside the region of Southern Denmark. Because there is no reason to believe that those who moved were at a higher or lower risk of getting cancer or dying, this should not influence the results.

This study did not include stage of the interval cancers; thus, it is unknown if a 1-year increase in screening interval could lead to more advanced cancers.

▲ **Table 3** CRC incidence in individuals with a FIT value < 10 µg/g feces screened in 2014 and 2015 after 2 and 3 years, respectively, with CRC. Pr. 1000 py.

		2-year follow-up				3-year follow-up			
FIT value (µg/g feces)	Individuals (%) (n = 121,855)	CRC (%) (n = 83)	HR (95 % CI)	Py	CRC pr. 1000 py (95 % CI)	CRC (%) (n = 173)	HR (95 % CI)	Py	CRC pr. 1000 py
< 4	113,328 (93.0)	56 (0.05)	Ref	225605.6	0.25 (0.19;0.32)	135 (0.12)	Ref	337343.5	0.40 (0.34;0.47)
4–6.9	5,918 (4.9)	16 (0.27)	4.617[1] (2.64;8.07)	11709.9	1.37 (0.78;2.22)	25 (0.42)	3.017[1] (1.97;4.63)	17458.3	1.43 (0.93;2.11)
7–9.9	2,609 (2.1)	11 (0.42)	6.970[1] (3.64;13.33)	5161.9	2.13 (1.06;3.81)	13 (0.5)	3.451[1] (1.95;6.10)	7671.6	1.70 (0.90;2.90)
Total	121,855	83 (0.07)		242477.4	0.34 (0.27;0.42)	173 (0.14)		362473.4	0.48 (0.41;0.55)

CRC, colorectal cancer; FIT, fecal immunochemical test; HR, hazard ratio; py; person-years; CI, confidence interval; ref, reference.
[1] Significant at a 5 % level.

Conclusions

This study found the overall incidence of interval CRC to be 0.07 % (0.34 CRC pr. 1000 person-years) in a 2-year screening round in FIT-negative individuals with a FIT < 10 µg/g feces, with increasing HRs for interval CRC corresponding to increasing FIT values. Increasing the follow-up by 1 year to 3 years, the overall incidence doubled to 0.14 %; however, the HRs were not significantly different. This could suggest that a longer screening interval could be safe and sensible in the low FIT categories. More studies are needed to confirm this as the incidence of CRC is so low that large populations are needed to create valid data.

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Competing interests

The authors declare that they have no conflict of interest.

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