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Significant decrease in interval colorectal cancer incidence after implementing immunochemical testing in a multiple-round guaiac-based screening programme

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SUMMARY

Background & aims: We aimed to evaluate the effects of switching to faecal immunochemical testing (FIT) on the cumulative 2-year incidence rate of interval cancers, interval cancer rate, and test sensitivity within a mature population-based colorectal cancer screening programme consisting of 6 rounds of biennial guaiac faecal occult blood testing (gFOBT).

Methods: The FIT results were compared with those of gFOBT used in each of the previous two rounds. For the 3 rounds analyzed, 279 041 tests were performed by 156 186 individuals. Logistic regression analysis was used to determine interval cancer risk factors (Poisson regression) and to compare the sensitivity of FIT to gFOBT.

Results: There were 612 cases of screen-detected cancers and 209 cases of interval cancers. The sex- and age-adjusted cumulative 2-year incidence rates of interval cancers were 55.7 (95% CI, 45.3-68.5), 42.4 (95% CI, 32.6-55.2), and 15.8 (95% CI, 10.9-22.8) per 100 000 person-years after the last two rounds of gFOBT and FIT, respectively. The FIT/gFOBT incidence rate ratio was 0.38 [95% CI, 0.27-0.54] ($P<0.001$). Sex- and age-adjusted sensitivity was significantly higher with FIT than with gFOBT (OR=6.70 [95% CI, 4.48-10.01], $P<0.0001$).

Conclusions: This population-based study revealed a dramatic decrease in the cumulative incidence rates of interval cancers after switching from gFOBT to FIT. These data provide an additional incentive for countries still using gFOBT to switch to FIT.

Keywords: interval colorectal cancer, colorectal cancer screening, faecal immunochemical test, guaiac faecal occult blood test

INTRODUCTION

Colorectal cancer (CRC) remains the second leading cause of cancer death worldwide, despite the declining mortality rates in North America and Northwest Europe.^{1,2} In the latter areas, screening programmes have been widely implemented, but death can occur when patients are not screened or inadequately followed up or when the screening test has failed.³ One of the ways in which failure is expressed is through the emergence of interval colorectal cancers (In-CRC); In-CRC has been defined internationally as CRC diagnosed after a screening or surveillance examination in which no cancer was detected but before the next recommended examination date.⁴ For screening with a biennial faecal occult blood test (FOBT), In-CRC is defined as a cancer detected after a negative screening test and before the next scheduled invitation two years later.⁴ The rate of occurrence is strongly correlated with the sensitivity of the screening test used and reflects the quality of the screening programme.⁵ Faecal immunochemical testing (FIT), compared with guaiac-FOBT (gFOBT), has been shown to increase participation and to increase cancer detection in randomized controlled trials and population-based screening programmes.⁶⁻⁸ The evidence that FIT decreases the incidence of In-CRC compared to gFOBT is based on comparison of studies where a single test was used or where the analysis of gFOBT and FIT arms was undertaken.⁹ However, little is known about the benefits of implementing FIT in an already established gFOBT-based screening programme, especially in regard to the incidence and characteristics of In-CRCs, which are data that may be important in the context of test switching in countries where gFOBT is still offered as the first-line screening test.^{8,10} Therefore, the aim of the present study was to retrospectively evaluate the benefits of switching from gFOBT to FIT in a long-term, 6-round, gFOBT-based screening programme. We have previously reported on the increased participation and diagnostic yield of such a switch,¹¹ but in this study, we sought to evaluate the incidence rates and characteristics of In-CRCs recorded after one FIT-based round and to compare them with those observed after each of the previous two gFOBT-based rounds.

POPULATION AND METHODS

The screening programme and study population

In 2003, the French national screening programme based on a biennial gFOBT (Hemoccult II; Beckman Coulter Inc., Villepinte, France) was fully implemented in 'Ille-et-Vilaine' in western France. CRC screening was proposed for individuals aged between 50 and 74 years with an average risk of CRC and no contraindications for colonoscopy. Individuals with a personal or family history of CRC or adenoma, individuals with inflammatory bowel disease, and individuals who had undergone total colonoscopy in the previous five years were excluded from the mass screening programme. The

target population of the CRC screening programme was defined as the population aged 50 to 74 years minus the excluded individuals.

The transition from gFOBT to FIT occurred in 'Ille-et-Vilaine' in May 2015; the FIT selected by the French Health Authorities was the OC-Sensor™ test (Eiken, Tokyo, Japan). Thus, six rounds of gFOBT-based screening and one round of FIT-based screening were performed between 2003 and 2017. gFOBT was defined as positive when one to six square(s) were positive, and a cutoff value of 30 µg of haemoglobin per gram of faeces (i.e., 150 ng of haemoglobin per milliliter of buffer) was used for FIT positivity. All positive individuals were recommended to undergo a colonoscopy, while those with negative tests were informed to participate again every two years until they were 74 years old. More details on the screening process data have been reported previously.^{11,12}

Because the 6th gFOBT-based round was somewhat shortened due to national public health decisions related to test switching, we also chose to include the 5th round in the present study for comparison with the 7th FIT-based round.

Data collection and outcome measures

The screening centre (ADECI 35) was responsible for recording exclusions, inviting the target population, and reminding them to enroll in the study if they did not participate after an initial letter. The centre also prospectively recorded all data regarding participation, FOBT results, and if positive, colonoscopy compliance and findings. Lesions found during colonoscopy and the corresponding treatment were prospectively recorded in the database, and these data were submitted by the gastroenterologists. Since the implementation of CRC screening in 2003, all pathology laboratories in the district and adjacent districts were required to send the details (first name, last name, date of birth) of all patients 50 years of age and older diagnosed with CRC to the screening centre, allowing the screening centre to cross-reference all CRCs diagnosed in patients with a negative test in 'Ille-et-Vilaine'. An In-CRC was defined as a CRC that was noted clinically within two years in any one of the individuals with a negative test, gFOBT or FIT. Details of In-CRC patients and their tumours (location, stage) were collected retrospectively from general practitioners, gastroenterologists and surgeons.

The age of patients with screen-detected CRCs (SD-CRCs) and In-CRCs was classified into 3 categories: <60 yrs, 60-69 yrs, and ≥70 yrs. Tumours were categorized according to the TNM staging system from stage 0 to IV, according to the UICC/AJCC classification.¹³ Stage 0 tumours corresponded to neoplasms with intramucosal infiltration, while intraepithelial tumours were excluded from the present study. The location of tumours was classified into 3 categories: proximal for tumours located beyond the splenic flexure, distal for those located between the rectosigmoid junction and the splenic flexure, and the rectum.

The main outcomes were the cumulative 2-yr incidence of In-CRCs, the In-CRC rate and the sensitivity of the test used, gFOBt or FIT. The cumulative incidence of In-CRCs was expressed as the number of In-CRCs per 100 000 persons-years among those with a negative test. The In-CRC rate was calculated by dividing the number of In-CRCs by the sum of SD-CRCs and In-CRCs while FOBt sensitivity was calculated by dividing the number of SD-CRCs by the sum of SD-CRCs and In-CRCs.

The secondary outcomes were a comparison of the characteristics of In-CRCs between the 3 rounds and with those of SD-CRCs. Moreover, we aimed to assess the consequences of lowering the threshold of positivity on FIT performance.

Statistical analysis

Quantitative variables were expressed as the means and standard deviations (SDs) or medians and interquartile ranges (IQRs) and were compared with the t-test (or ANOVA if >2 groups) or Mann-Whitney-Wilcoxon test (or Kruskal-Wallis if >2 groups). Qualitative variables were expressed as numbers or percentages and were compared with the χ^2 test or Fisher's test. For comparisons between 3 groups, if the test was significant ($p < 0.05$), 2-to-2 comparisons, with correction according to the Bonferroni or Dwass-Steel-Critchow-Fligner method, were performed. Test sensitivity estimates were expressed as percentages with 95% confidence intervals (CIs), compared between the 3 rounds using logistic regression, and tested for significant variables by Tukey adjustment for 2-to-2 comparisons. Analyses were performed for the total population and after exclusion of stage 0 cancers from SD- and In-CRCs. To further assess factors associated with In-CRC occurrence among negatives, a univariate Poisson regression model was used. Potential covariates ($p < .20$) were placed into a multivariate Poisson regression model, and stepwise backward elimination was performed. The rate ratios and corresponding 95% CIs were used to express the association between the studied factors and the In-CRC cumulative incidence. We sought to determine the sensitivity of the FIT if the screening programme had adopted a lower test positivity threshold of 20 and 10 $\mu\text{g/g}$, so that we could compare our results with those of screening programmes that had adopted such thresholds. The number of individuals needed to undergo colonoscopy was also determined to find one more cancer at these latter thresholds. All analyses were performed using the statistical software programme SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA). A test was interpreted as significant if the p value was < 0.05 . All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Population of screen-detected and interval cancers

The main characteristics of the 3 rounds considered in the analyses are given in **Table 1**. A total of 279 041 tests were performed by 156 186 individuals in rounds 5, 6 and 7. There were 612 cases of SD-CRC and 209 cases of In-CRC, for a total of 821 cases of CRC. The comparative characteristics of the two types of cancers are given in **Table 2**. When compared with SD-CRCs, In-CRCs were more likely to be proximal and rectal tumours, were less likely to be distal tumours, and were more often advanced cancers (stage III/IV). In addition, among patients with In-CRC, the proportion of women was increased, and the proportion of individuals participating for the first time was less than that among SD-CRC patients (**Table 2**).

Cumulative incidence of interval cancers

The number of In-CRCs was 99, 62 and 48 in rounds 5, 6 and 7, respectively, corresponding to cumulative 2-year incidence rates of 55.7 (95% CI, 45.3-68.5), 42.4 (95% CI, 32.6-55.2), and 15.8 (95% CI, 10.9-22.8) per 100 000 person-years after adjusting for sex and age. By multivariate analysis (Poisson regression), increasing age, sex (men versus women), screening rank (subsequent versus first screening), and the test used (gFOBT versus FIT) were the factors significantly associated with the incidence rate of In-CRCs among those with negative testing (**Table 3**). Thus, the FIT/gFOBT incidence rate ratio was 0.38 [95% CI, 0.27-0.54] using round 5 as the reference. By analyzing the FIT-based round separately by multivariate analysis, the 3 factors significantly associated with an increase in the incidence rate of In-CRCs were increasing age, the season for testing (spring/summer versus autumn/winter), and the faecal haemoglobin level (**Table 3**). The cumulative 2-year incidence rates of In-CRCs were 198.44 [95% CI, 119.6-329.2] per 100 000 person-years for a haemoglobin level between 10 and 19 $\mu\text{g/g}$ and 275.6 [95% CI, 137.8-551.1] per 100 000 person-years for a haemoglobin level between 20 and 29 $\mu\text{g/g}$, contrasting with the rate of 11.6 [95% CI, 7.8-17.2] per 100 000 person-years for cutoff values below 10 $\mu\text{g/g}$.

Interval cancer rate and test sensitivity estimates

The In-CRC rate was 44.0% and 44.6% in the two gFOBT-based rounds and 10.5% in the FIT-based round (**Table 1**), reflecting test sensitivities for CRC detection of 56.0%, 55.4% and 89.5%, respectively ($P < 0.0001$). Test sensitivity estimates after adjusting for sex and age, rank of screening, season for testing, and tumor location are given in **Table 4**. The results of the logistic regression analysis comparing the sensitivity of FIT to that of gFOBT are given in **Table 5**. FIT sensitivity was

significantly higher than that of gFOBT as measured in the two previous rounds, regardless of the variable analyzed, including sex, age, season for screening, tumor location, and rank of screening, except for the first screening category in the fifth round (**Table 5**). The gFOBT sensitivity estimates did not differ between the two gFOBT-based rounds, except for the distal location of CRCs (data not shown). After excluding stage 0, CRCs from the total population did not change the comparative results of FIT and gFOBT sensitivities, as shown by the odds ratios of 6.9 [95% CI, 4.4-10.9] and 7.5 [95% CI, 4.5-12.6] for rounds 5 and 6, respectively.

Characteristics of interval cancers compared between gFOBT- and FIT-based rounds

As expected because most participants at each round had already been tested in the previous rounds, the age of patients at the time of testing and In-CRC diagnosis, as well as the screening rank, were higher in the FIT-based round than in the previous two rounds (**Table 6**). However, there were no significant differences between the 3 rounds in the proportion of never-screened versus previously screened participants, in the time between negative testing and In-CRC diagnosis, in the proportion of In-CRCs diagnosed in the first or second year after negative testing, or in the distribution of cancer location and stage (**Table 6**).

Consequences of lowering the cutoff value for FIT positivity

If a lower threshold of positivity had been chosen by the programme, it can be presumed that 8 cases of In-CRC at the threshold of 20 µg/g and another 15 at the threshold of 10 µg/g would have been detected at an earlier stage. At the threshold of 20 µg/g FIT, sensitivity would have increased from 89.5% [95% CI, 86.7%; 92.3%] to 91.3% [88.6%; 93.8%] and to 94.5% [95% CI, 92.4%; 96.6%] at the threshold of 10 µg/g. The 23 In-CRCs that would have been prevented at the threshold of 10 µg/g represented 48% of all In-CRCs occurring at the threshold of 30 µg/g, but only 5.6% of the cancers screened at the threshold of 30 µg/g. The number needed for colonoscopy to find one CRC more from 10 to 30 µg/g would have been 228 individuals, assuming that no other cancers, other than In-CRCs, would have been found at colonoscopy.

DISCUSSION

The primary objective of the present study was to evaluate the benefit of switching from gFOBT to FIT in a long-term, 6-round, gFOBT-based screening programme on the In-CRC incidence rate. We previously reported that the switch from gFOBT to FIT was responsible for a fivefold increase in the detection of cancer, an increased participation of nearly 20%, a higher test positivity rate, and a higher positive predictive value for cancer;¹¹ these results are consistent with those from

other screening centres in France.^{14,15} In England, a pilot study with FIT within the established national screening programme also reported markedly improved participation and neoplasia detection, but In-CRCs were not assessed in that study.¹⁶ Thus, a decrease in the occurrence of In-CRC after switching was expected, but this remains to be proven in a mature programme. Our study showed that the cumulative 2-year incidence rate of In-CRC, adjusted for sex and age, was 15.8 [95% CI, 10.9-22.8] per 100 000 person-years for the FIT and 55.7 [95% CI, 45.3-68.5] and 42.4 [95% CI, 32.6-55.2] per 100 000 person-years for the gFOBT. These values are very similar to those reported in a meta-analysis restricted to high-quality studies, with 15 (95% CI, 8-30) and 55 (95% CI, 35-87) per 100 000 person-years for FIT and gFOBT, respectively.⁹ Of note, our findings for FIT were also very similar to those recently reported in Italy based on a population followed for 13 years with FIT repeated every two years (1.87 per 10 000 person-years).¹⁷ To our knowledge, the only previous study that reported a benefit of switching from gFOBT to FIT on the incidence of In-CRC within a screening programme is a Belgian study, in which the incidence rates for gFOBT and FIT In-CRCs were higher at 21.3 and 4.9 per 10 000 person-years, respectively.¹⁸ However, whereas in the Belgian study the comparison of both tests was made on the occasion of a first screening, our study is more consistent with real life, with a large majority of people already screened among the participants at each round analyzed here. In the Belgian study,¹⁸ the incidence rate ratio between FIT- and gFOBT In-CRCs was 0.23 versus 0.36, respectively, in the meta-analysis that analyzed three studies that compared gFOBT and FIT in two arms.⁹ In the present study, the incidence rate ratio between FIT- and gFOBT In-CRCs was 0.38 [95% CI, 0.27-0.54] when taking round 5 as the reference in the multivariable analysis. Factors significantly associated with the In-CRC incidence rate in our study, other than the test, were increasing age, sex (men over women), and rank of screening (subsequent over first screening). However, when analyzing the FIT-based round separately, the only significant factors were increasing age, season for screening, and faecal haemoglobin level. The role of aging has already been demonstrated.^{9,19-21} Seasonal variations in the In-CRC risk were reported in a Korean study with different FITs, including the OC-Sensor™ test at a cut-off of 20 µg/g, with an odds ratio of 1.31 for the summer months, highlighting the role of temperature on haemoglobin stability.²² We have to be careful when interpreting our results because of the very wide confidence intervals. Other studies conducted in France, such as ours (data not shown), have not shown seasonal variations in the rate of FIT positivity, but the rate of In-CRC has not been investigated in these studies.^{23,24}

Unlike the cumulative incidence rate, which was calculated from negative tests, the calculation of the In-CRC rate depended on the number of SD-CRCs and consequently on the test positivity rate, its positive predictive value for CRC diagnosis and the colonoscopy compliance. In the present study, the In-CRC rate was quite similar in the two gFOBT-based rounds (44.0%, 44.6%), i.e.,

approximately 4-fold higher than in the FIT-based round (10.5%). In our gFOBT-based screening programme that started in 2003, the In-CRC rate was 33% in the first round and 40% in the second round (data not shown). Very similar data were recorded thereafter, highlighting the role that the switch from gFOBT to FIT plays in the dramatic decrease reported here. Because the sensitivity of the screening test is an inverse function of the interval cancer rate, the age- and sex-adjusted sensitivity estimates in this study were 54.5% and 55.4% for gFOBT and 88.6% for FIT. In two recent meta-analyses, FIT sensitivity estimates for CRC detection ranged from 69% to 80% and 77% to 94% depending on the positivity threshold.^{25,26} Corresponding values at the cutoff of 15 µg/g were 84% and 90.5% in two recent studies from Belgium and the Netherlands.^{18,27} In the present study, we showed that lowering the positivity threshold from 30 to 10 µg/g faeces would have transformed 48% of In-CRCs (23 cases) into as many SD-CRCs and thus increased the sensitivity of FIT for CRC by 5%. Nevertheless, detection of these 23 cases would have required more than 5000 colonoscopies, i.e., more than what was needed to detect the 409 cancers at a positivity threshold of 30 µg/g, which seems disproportionate and validates *a posteriori* the choice of the 30 µg/g threshold made by the French programme. As expected, the present study demonstrates a higher sensitivity of FIT on gFOBT regardless of age, sex, screening rank, season for screening, and cancer location. Regarding the sensitivity of the tests according to cancer location, which has been the subject of controversy in the literature, our results are in agreement with those of two recent meta-analyses that concluded that gFOBT and FIT have better diagnostic performance for detecting cancers in the distal colon than in the proximal colon.^{28,29} Not surprisingly, comparison of In-CRC characteristics between the 3 rounds of this study showed no significant difference in the distribution of cancer location and a predominance of proximal and rectal location. The only significant difference between participant characteristics with In-CRCs was the higher age of participants at the time of testing and CRC diagnosis of In-CRCs after FIT, simply related to the aging of a population that has already participated in previous gFOBT-based rounds, as also evidenced by the higher screening rank. When analyzing participant and tumour characteristics according to In- and SD-CRCs, In-CRCs occurred more often in women, were less frequent after a first screening, had more frequent proximal and rectal locations and had more frequent advanced stages, in agreement with gFOBT and FIT literature data.³⁰⁻³³

Our study has several limitations. First, it was a retrospective study, but nevertheless, missing data were limited to 5.6% and 0.7% of the population for cancer stage and location, respectively. Second, our region does not have a cancer registry, which could theoretically lead to missing some In-CRCs in the event of medical care outside the region or emigration. However, if such a problem exists, it is certainly marginal, as is its net effect on the comparison between tests. Third, it has

recently been stated that the test sensitivity should be measured with the proportional In-CRC rate method rather than the In-CRC proportion method, which means that the incidence rate of In-CRCs in population-based screening programmes should be analyzed in relation to the expected incidence rate of CRC in background populations.^{17,34,35} However, in the recent study by Zorzi et al,¹⁷ only small differences were shown between the FIT sensitivity for cancer detection measured by either method (86.9% versus 83.9%). Fourth, our study did not take into account potential CRCs occurring in positive individuals who did not undergo colonoscopy (less than 7% in each of the 3 rounds) or the cancers diagnosed after colonoscopy, also called post-colonoscopy In-CRCs. Thus, the sensitivity measured in our study was the sensitivity of the test, not the sensitivity of the programme. Fifth, we could be criticized for including intramucosal cancers (stage 0 CRC), which are noninvasive cancers, in this study. However, it is standard practice in France to count them among SD-CRCs.³⁶ In any case, the analysis excluding stage 0 CRCs from this study showed no change in the test sensitivity results. Sixth, in searching risk factors for In-CRC among negatives, we were unable to examine the burden of participant factors such as smoking, diabetes, hypertension and obesity, which were previously identified in a meta-analysis as increasing the risk of false-negative FIT, because dietary or lifestyle patterns of participants in our study were not recorded.¹⁹

To conclude, this population-based study demonstrated a dramatic decrease in the cumulative incidence rate of In-CRCs after switching from gFOBT to FIT within an established mature CRC screening programme. Our study demonstrates the higher sensitivity of FIT compared to gFOBT regardless of age, sex, screening rank (except first screening), season for screening and cancer location. These data provide an additional incentive for countries still using gFOBT to switch to FIT.

ADDITIONAL INFORMATION

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- **AUTHORS' CONTRIBUTIONS**

Conception and design (JFB, CP, MC, AL); analysis and interpretation of the data (CR, JFB, AL, AC, CP, MC); drafting of the article (JFB, AL); all of the authors approved the final manuscript.

- **ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

The colorectal cancer screening programme was declared and approved by the CNIL (Commission Nationale de l'Informatique et des Libertés) on August 30, 2002 (no. 812571). This research was approved by the CCTIRS (Comité Consultatif pour le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé).

- **CONSENT FOR PUBLICATION**

Not applicable

- **DATA AVAILABILITY**

The authors state that the data from their study are available on request from the Biostatistics Department of the University Hospital Center of Rennes. chloe.rousseau@chu-rennes.fr

- **COMPETING INTERESTS**

The authors declare no conflict of interest.

- **FUNDING INFORMATION**

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Table 1. Main characteristics of the populations of the two gFOBT-based rounds (5, 6) and the FIT-based round (7)

	Round 5 gFOBT 2010-2012	Round 6 gFOBT 2012-2014	Round 7 FIT 2015-2017
Total population at the start of the round (million inhabitants)	0.996	1.019	1.042
Population aged from 50 to 74 years, n	249 573	258 994	269 698
Target population, n	212 112	214 540	223 374
Men, n	101 200	102 651	107 010
Women, n	110 912	111 889	116 364
Population participating in the screening programme, n (%)			
Total, n (%)	87 126 (41.1%)	72 642 (33.9%)	119 272 (53.4%)
Men, (%)	39 466 (39.0%)	33 010 (32.2%)	55 410 (51.8%)
Women, n (%)	47 660 (43.0%)	39 632 (35.4%)	63 862 (54.9%)
Positive testing, n (%)	1926 (2.2%)	1651 (2.3%)	5084 (4.3%)
<ul style="list-style-type: none"> Colonoscopy, n (%) 	1798 (93.4%)	1536 (93.0%)	4735 (93.1%)
Estimates per 100 000 attendees, n	2063	2273	3970
<ul style="list-style-type: none"> Screen-detected cancer, n (%)* 	126 (7.0%)	77 (5.0%)	409 (8.6%)
<ul style="list-style-type: none"> NNScope for cancer **, n 	14.3	19.9	11.6
Negative testing, n	84 762	69 272	112 881
<ul style="list-style-type: none"> Individuals with interval cancer, n 	99	62	48
<ul style="list-style-type: none"> Interval cancer rate, %*** 	44.0%	44.6%	10.5%

* Percentage of screen-detected cancers among individuals who underwent colonoscopy

** Number of individuals needed to scope to detect one case of cancer

*** Interval cancer rate=sum of interval cancers/sum of interval cancers and screen-detected cancers

Table 2. Comparison of participant and tumour characteristics among subjects with screen-detected cancer or interval cancer

Variable	Screen-detected	Interval cancers	P
	cancers n=612	n=209	
Round, n (%)	612 (0)	209 (0)	<0.0001
Round 5	126 (20.6%)	99 (47.4%)	
Round 6	77 (12.6%)	62 (29.7%)	
Round 7	409 (66.8%)	48 (23.0%)	
Sex, n	612 (0)	209 (0)	0.0030
Women	219 (35.8%)	99 (47.4%)	
Men	393 (64.2%)	110 (52.6%)	
Age at screening, yrs mean ± SD	611 (1) 64.4 ± 6.7	209 (0) 64.2 ± 6.4	0.6110
Age at screening, yrs	611 (1)	209 (0)	0.9615
<60	164 (26.8%)	57 (27.3%)	
60-69	302 (49.4%)	101 (48.3%)	
≥70	145 (23.7%)	51 (24.4%)	
Age at diagnosis, yrs mean ± SD	607 (5) 64.7 ± 6.7	209 (0) 65.2 ± 6.4	0.3062
Time between screening and diagnosis, months median (IQR)	608 (4) 1.8 (1.3; 2.7)	209 (0) 13.2 (6.1; 17.9)	<0.0001
Time between screening test result and diagnosis of colorectal cancer	608 (4)	209 (0)	<0.0001
1-12 months	592 (97.4%)	95 (45.5%)	
13-24 months	16 (2.6%)	114 (54.5%)	
Screening rank median (IQR)	612 (0) 5 (4; 7)	209 (0) 5 (4; 6)	0.0070
Screening rank (category)	612 (0)	209 (0)	0.0292
First	47 (7.7%)	7 (3.3%)	
Subsequent	565 (92.3%)	202 (96.7%)	
Season for screening	612 (0)	209 (0)	0.2061
Spring	148 (24.2%)	59 (28.2%)	
Summer	139 (22.7%)	48 (23.0%)	
Autumn	176 (28.8%)	45 (21.5%)	
Winter	149 (24.3%)	57 (27.3%)	
Tumour location	610 (2)	205 (4)	0.0001
Distal	292 (47.9%)	62 (30.2%)	
Proximal	164 (26.9%)	74 (36.1%)	

Rectal	154 (25.2%)	69 (33.7%)	
Tumour stage	585 (27)	190 (19)	<0.0001
0	151 (25.8%)	23 (12.1%)	
I	194 (33.2%)	36 (18.9%)	
II	91 (15.6%)	43 (22.6%)	
III	109 (18.6%)	46 (24.2%)	
IV	40 (6.8%)	42 (22.1%)	
Tumour stage (category)	585 (27)	190 (19)	<0.0001
0/I/II	436 (74.5%)	102 (53.7%)	
III/IV	149 (25.5%)	88 (46.3%)	
Cellular differentiation	441 (20)	177 (9)	0.1494
Well-differentiated	343 (77.8%)	128 (72.3%)	
Moderately/poorly differentiated	98 (22.2%)	49 (27.7%)	

The number of individuals with missing data is indicated in parentheses on the first horizontal line for each variable.

Table 3. Factors significantly associated with the cumulative incidence rate of interval cancers among negative individuals by multivariate analysis (Poisson regression)

Variables	Incidence rate per 100 000 person- years	Rate ratio (95% CI)	p	2 to 2 comparison with Tukey adjustment P
Pooled analysis of the 3 rounds				
Rounds				Round 7 vs round 5 <0.0001
Round 5 (gFOBT)	58.4 [47.9-71.1]	1	<0.0001	Round 7 vs round 6 0.0003
Round 6 (gFOBT)	44.7 [34.9-57.4]	0.77 [0.56-1.06]		Round 6 vs round 5 0.227
Round 7 (FIT)	21.3 [16.0-28.2]	0.38 [0.27-0.54]		
Sex				
Women	34.0 [27.9-41.4]	1	0.0286	
Men	45.2 [37.5-54.5]	1.35 [1.03-1.78]		
Age at screening				[60-69] vs ≥ 70 yrs 0.0408
<60 years	23.9 [18.5-31.1]	1	<0.0001	[60-69] vs < 60 yrs 0.0003
60-69 years	45.5 [37.4-55.3]	1.62 [1.16-2.26]		≥ 70 vs < 60 yrs <0.0001
≥70 years	69.0 [52.4-90.7]	2.43 [1.65-3.57]		
Screening rank				
First screening	10.5 [5.0-22.1]	1	0.0152	
Subsequent screening	43.2 [37.6-49.6]	2.62 [1.20-5.71]		
Separate analysis of the FIT-based round (round 7)				
Age at screening				[60-69] vs ≥ 70 yrs 0.0011
<60 yr	7.6 [3.8-15.3]	1	<0.0001	[60-69] vs < 60 yrs 0.0317
60-69 yr	21.9 [14.1-33.9]	2.58 [1.14-5.87]		≥ 70 vs < 60 yrs <0.0001
≥70 yr	67.2 [43.4-104.2]	7.30 [3.21-16.62]		
Haemoglobin level				10-19 vs 20-29 µg/g 0.7335
<10 µg/g	11.6 [7.8-17.2]	1	<0.0001	10-19 vs < 10 µg/g < 0.0001
10-19 µg/g	198.4 [119.6-329.2]	15.33 [8.07-29.1]		20-29 vs < 10 µg/g < 0.0001
20-29 µg/g	275.6 [137.8-551.1]	20.59 [9.27-45.7]		
Season for screening				
Autumn/winter	15.2 [9.8-23.5]	1	0.0492	
Spring/summer	29.8 [20.5-43.1]	1.78 [1.00-3.16]		

Table 4. Test sensitivity for cancer detection in the 3 rounds according to age and sex and other variables adjusted for age and sex (rank of screening, season for screening, tumour location)

Variables	Round 5	Round 6	Round 7
	gFOBT mean [95% CI]	gFOBT mean [95% CI]	FIT mean [95% CI]
Sex			
Men	62.9% [54.5-71.2%]	55.2% [44.5-65.8%]	92.3% [89.1-95.4%]
Men adjusted for age	62.9% [54.5-71.3%]	55.2% [44.5-65.9%]	92.25% [89.1-95.4%]
Women	46.2% [35.9-56.6%]	55.8% [41.8-69.7%]	85.0% [79.6-90.4%]
Women adjusted for age	46.2% [35.9-56.5%]	55.77% [42.8-68.7%]	84.9% [79.5-90.3%]
Age			
Age <60 yrs	58.3% [45.5-71.2%]	41.46% [25.7-57.2%]	93.3% [88.8-97.9%]
Age <60 yrs adjusted for sex	51.2% [37.9-64.5%]	40.0% [24.4-55.6%]	92.9% [88.3-97.4%]
Age 60-69 yrs	52.1% [43.0-61.2%]	65.2% [53.7-76.7%]	90.7% [86.8-94.6%]
Age 60-69 yrs adjusted for sex	51.8% [42.6-60.9%]	67.2% [54.8-79.6%]	89.8% [85.6-94.0%]
Age ≥70 yrs	63.0% [48.6-77.5%]	51.7% [32.4-71.1%]	83.5% [76.8-90.2%]
Age ≥70 yrs adjusted for sex	62.2% [47.8-76.6%]	53.9% [34.5-73.3%]	82.7% [75.9-89.4%]
Age and sex			
Adjusted for age and sex	54.5% [47.9-61.1%]	55.4% [46.8-64.1%]	88.6% [85.7-91.5%]

Rank of screening			
First screening age- and sex-adjusted	84.3% [39.4-100.0%]	83.8% [21.5-100.0%]	95.5% [89.1-100.0%]
Subsequent screening age- and sex-adjusted	53.8% [47.2-60.5%]	54.5% [45.6-63.4%]	88.0% [84.9-91.1%]
Season for screening			
Spring age- and sex-adjusted	51.9% [39.2-64.6%]	63.4% [46.9-79.8%]	83.8% [77.0-90.5%]
Summer age- and sex-adjusted	61.1% [45.4-76.9%]	37.5% [17.0-58.0%]	86.5% [80.3-92.7%]
Autumn age- and sex-adjusted	56.1% [43.3-68.8%]	58.1% [38.5-77.8%]	92.0% [87.3-96.7%]
Winter age- and sex-adjusted	50.7% [37.6-63.8%]	57.1% [40.1-74.2%]	90.8% [85.0-96.5%]
Tumour location			
Distal colon cancer age- and sex-adjusted	70.6% [61.1-80.2%]	51.4% [37.1-65.7%]	95.4% [92.3-98.4%]
Proximal colon cancer age- and sex-adjusted	45.00% [33.2-56.8%]	67.0% [51.6-82.3%]	82.5% [75.8-89.2%]
Rectum age- and sex-adjusted	41.5% [28.4-54.6%]	48.3% [30.3-66.4%]	85.0% [78.7-91.3%]

Table 5. Logistic regression comparison of FIT versus gFOBt sensitivity by participant and tumour characteristics (with Tukey adjustment)

Population	N	OR [95% CI] round 5 (gFOBt)	OR [95% CI] round 6 (gFOBt)	P round 5	P round 6
Total population	821	6.69 [4.49-9.97]	6.86 [4.38-10.74]	<0.0001	<0.0001
Total population, age- and sex-adjusted	820	6.70 [4.48-10.01]	7.01 [4.46-11.03]		
Sex					
Men	503	7.03 [3.59-13.76]	9.68 [4.68-20.01]	<0.0001	<0.0001
Men, age-adjusted	503	7.22 [4.11-12.69]	9.86 [5.36-18.14]		
Women	317	6.57 [3.27-13.22]	4.48 [1.97-10.22]	<0.0001	<0.0001
Women, age-adjusted	317	6.63 [3.69-11.90]	4.46 [2.24-8.90]		
Age					
< 60 years	221	10.00 [3.48-28.77]	19.76 [6.34-61.60]	<0.0001	<0.0001
< 60 years, sex-adjusted	221	13.23 [5.17-33.84]	23.23 [8.57-62.96]		
60-69 years	403	8.96 [4.45-18.05]	5.20 [2.31-11.69]	<0.0001	<0.0001
60-69 years, sex-adjusted	403	8.77 [4.88-15.76]	5.22 [2.65-10.27]		
≥ 70 years	196	2.96 [1.18-7.42]	4.71 [1.66-13.40]	0.0157	0.0015
≥ 70 years, sex-adjusted	196	2.95 [1.37-6.39]	4.82 [2.00-11.62]		
Rank of screening					
First screening	54	11.00 [0.52-234.29]	16.50 [1.02-266.88]	0.1571	0.0479
First screening, age- and sex-adjusted	54	10.84 [0.82-143.39]	15.68 [1.44-171.18]		
Subsequent screening	767	6.47 [3.98-10.50]	6.72 [3.86-11.70]	<0.0001	<0.0001
Subsequent screening, age- and sex-adjusted	766	6.41 [4.27-9.64]	6.78 [4.25-10.80]		
Season for screening					
Spring	207	5.86 [2.40-14.30]	3.75 [1.33-10.59]	<0.0001	0.0081
Spring, age- and sex-adjusted	206	5.67 [2.67-12.04]	3.53 [1.47-8.50]		
Summer	187	4.48 [1.65-12.21]	11.92 [3.89-36.55]	0.0013	<0.0001
Sommer, age- and sex-adjusted	187	4.38 [1.87-10.25]	12.97 [4.98-33.79]		
Autumn	221	8.27 [3.02-22.62]	8.48 [2.70-26.65]	<0.0001	<0.0001
Autumn, age- and sex-adjusted	221	8.61 [3.64-20.39]	9.39 [3.50-25.17]		
Winter	206	8.45 [3.17-22.54]	6.87 [2.33-20.32]	<0.0001	<0.0001
Winter, age- and sex-adjusted	206	8.41 [3.70-19.11]	6.86 [2.77-17.00]		
Tumour location					
Distal colon	354	8.00 [3.14-20.39]	19.26 [7.10-52.23]	<0.0001	<0.0001

Distal colon, age- and sex-adjusted	353	8.04 [3.66-17.64]	20.14 [8.65-46.89]		
Proximal colon	238	5.91 [2.66-13.14]	2.42 [0.95-6.17]	<0.0001	0.0691
Proximal colon, age- and sex-adjusted	238	6.09 [3.09-12.02]	2.65 [1.20-5.88]		
Rectum	233	7.49 [3.17-17.69]	6.71 [2.50-17.97]	<0.0001	<0.0001
Rectum, age- and sex-adjusted	223	7.97 [3.81-16.66]	7.24 [3.11-16.86]		

Table 6. Comparison of participant characteristics with interval cancer and of tumour characteristics between the 3 rounds

Variables	Round 5^a gFOBT n=99	Round 6^b gFOBT n=62	Round 7^c FIT n=48	P	P^{a,b}	P^{a,c}	P^{b,c}
Sex	99 (0)	62 (0)	48 (0)	0.1420			
Women	50 (50.5%)	23 (37.1%)	26 (54.2%)				
Men	49 (49.5%)	39 (62.9%)	22 (45.8%)				
Age at screening, yrs mean ± SD	99 (0) 63.7 ± 5.8	62 (0) 63.1 ± 7.0	48 (0) 66.5 ± 6.5	0.0153	1.0000	0.0442	0.0192
Age at cancer diagnosis, yrs (SD) mean ± SD	99 (0) 64.7 ± 5.8	62 (0) 64.1 ± 6.9	48 (0) 67.5 ± 6.5	0.0128	1.0000	0.0359	0.0166
Time between screening and cancer diagnosis, months median (IQR)	99 (0) 13.0 (6.1; 17.5)	62 (0) 13.0 (5.8; 19.6)	48 (0) 14.9 (6.1; 18.0)	0.6111			
Time between screening and cancer diagnosis (category)	99 (0)	62 (0)	48 (0)	0.6460			
0-11 months	47 (47.5%)	29 (46.8%)	19 (39.6%)				
12-24 months	52 (52.5%)	33 (53.2%)	29 (60.4%)				
Rank of screening, n (SD) median (IQR)	99 (0) 5.0 (4.0; 5.0)	62 (0) 6.0 (3.0; 6.0)	48 (0) 7.0 (5.0; 7.0)	<0.0001	0.0219	<0.0001	<0.0001
Rank of screening (category)	99 (0)	62 (0)	48 (0)	0.2799			
First screening	2 (2.0%)	4 (6.5%)	1 (2.1%)				
Subsequent screening	97 (98.0%)	58 (93.5%)	47 (97.9%)				
Season for screening	99 (0)	62 (0)	48 (0)	0.4291			

Spring	31 (31.3%)	14 (22.6%)	14 (29.2%)	
Summer	16 (16.2%)	18 (29.0%)	14 (29.2%)	
Autumn	22 (22.2%)	13 (21.0%)	10 (20.8%)	
Winter	30 (30.3%)	17 (27.4%)	10 (20.8%)	
Cancer location	98 (1)	60 (2)	47 (1)	0.0840
Distal colon	26 (26.5%)	26 (43.3%)	10 (21.3%)	
Proximal colon	39 (39.8%)	15 (25.0%)	20 (42.6%)	
Rectum	33 (33.7%)	19 (31.7%)	17 (36.2%)	
Cancer stage	94 (5)	54 (8)	42 (6)	0.3823
0	13 (13.8%)	3 (5.6%)	7 (16.7%)	
I	19 (20.2%)	10 (18.5%)	7 (16.7%)	
II	17 (18.1%)	12 (22.2%)	14 (33.3%)	
III	24 (25.5%)	14 (25.9%)	8 (19.0%)	
IV	21 (22.3%)	15 (27.8%)	6 (14.3%)	
Cancer stage (category)	94 (5)	54 (8)	42 (6)	0.1272
0/I/II	49 (52.1%)	25 (46.3%)	28 (66.7%)	
III/IV	45 (47.9%)	29 (53.7%)	14 (33.3%)	
Tumour differentiation	82 (4)	57 (2)	38 (3)	0.3595
Well-differentiated	61 (74.4%)	43 (75.4%)	24 (63.2%)	
Moderately/poorly differentiated	21 (25.6%)	14 (24.6%)	14 (36.8%)	

Number of individuals with missing data is given in brackets