Incidence of Interval Colorectal Cancer After Negative Results From First-Round Fecal Immunochemical Screening Tests, by Cutoff Value and Participant Sex and Age

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BACKGROUND & AIMS: We evaluated the incidence of interval cancers between the first and second rounds of colorectal cancer (CRC) screening with the FOB-Gold fecal immunochemical test (FIT), and the effects of different cutoff values and patient sex and age.

METHODS: We collected data from participants in a population-based CRC screening program in the Netherlands who had a negative result from a first-round of FIT screening. We calculated the cumulative incidence of interval cancer after a negative result from a FIT and the sensitivity of the FIT for detection of CRC at a low (15 μg Hb/g feces) and high (47 μg Hb/g feces) cutoff value.

RESULTS: Among the 485,112 participants with a negative result from a FIT, 544 interval cancers were detected; 126 were in the 111,800 participants with negative results from a FIT with the low cutoff value and 418 were in the 373,312 FIT participants with negative results from a FIT with the high cutoff value. The mean age of participants tested with the low cutoff value was 72.0 years and the mean age of participants tested the high cutoff value was 66.7 years. The age-adjusted 2-year cumulative incidence of interval cancer after a negative result from a FIT were 9.5 per 10,000 persons at the low cutoff value vs 13.8 per 10,000 persons at the high cutoff value ($P < .005$). The age-adjusted sensitivity of the FIT for CRC were 90.5% for the low cutoff value vs 82.9% for the high cutoff ($P < .0001$). The FIT identified men with CRC with 87.4% sensitivity and women with CRC with 82.6% sensitivity ($P < .001$).

CONCLUSIONS: In an analysis of data from a FIT population-based screening program in the Netherlands, we found that incidence of interval CRC after a negative result from a FIT to be low. Although the sensitivity of detection of CRC decreased with a higher FIT cutoff value, it remained above 80%.

Keywords: Colon Cancer; Screening; Fecal Immunochemical Testing; Interval Cancer.

[a]Authors share co-senior authorship.

Abbreviations used in this paper: AA, advanced adenoma; CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical test; Hb, hemoglobin.

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Many countries have introduced a screening program for colorectal cancer (CRC) in recent years. Different screening modalities are suitable for that purpose. Opportunistic screening programs most often use colonoscopy for primary screening, while organized population-based programs mostly prefer fecal immunochemical testing (FIT).[1] Colonoscopy has better test characteristics compared with FIT when applied for 1-time screening, yet is invasive, burdensome, and costly. FIT is noninvasive, nonburdensome, and less costly, but has lower test sensitivity.[2–4] For optimal program sensitivity and preventive effect, FIT should be repeated regularly.

FIT has been shown to be effective in detecting CRC at low cutoffs or short screening intervals.[5,6] Modeling studies suggested that by repeating FIT annually, with an assumed test sensitivity of 73.8% for CRC, the long-term preventive effect would be similar to colonoscopy screening.[5] The number of interval CRCs in the Dutch CRC screening pilot study was recently evaluated, based on 3 biennial FIT screening rounds. This relatively small study showed an interval CRC incidence rate of 0.1% and a sensitivity of 77% over 3 screening rounds.[6] However, these interval CRCs were observed while using a very low FIT cutoff of 10 μg hemoglobin (Hb)/g feces. In many regional or national population-based organized programs a higher cutoff for a positive FIT with referral to colonoscopy is chosen for a better balance between true and false positives.[1] Six months after the start of the Dutch national program, the FIT cutoff was increased from 15 to 47 μg Hb/g feces, because of a higher than expected positivity rate with an associated lower positive predictive value and shortage in colonoscopy capacity.[7] With this higher cutoff, we assumed that 12% of the CRCs would be missed, resulting in an relative decrease in sensitivity of 12%.[8]

Evaluation of the number of interval CRCs within organized population-based screening programs is important. The results of the Dutch CRC FIT-based screening program enable us to evaluate the number of interval CRCs after the first screening and determine the impact of using a relatively high vs a low FIT cutoff on the cumulative incidence and sensitivity of FIT for CRC.

What You Need to Know

Background

We evaluated the incidence of interval colorectal cancer (CRC) between the first and second rounds of screening (interval cancers) with a fecal immunochemical test (FIT) and the effects of different cutoff values, gender, and age.

Findings

In an analysis of data from the national FIT population-based screening program in the Netherlands, we found that incidence of interval CRC after a negative result from an FIT to be low. Although the sensitivity of detection of CRC decreased with a higher FIT cutoff value, it was above 80%.

Implications for patient care

Persons with a negative result from a screening FIT should be tested again at the recommended interval.

Materials and Methods

Screening Program and Population

In the Netherlands, a national population-based CRC screening program was implemented in 2014, with biennial FIT screening for persons 55–75 years of age. The program was rolled out in 5 years (2014–2018), with a phased implementation by age groups (birth cohorts). In 2014, individuals 60, 63, 65, 67, 75, and 76 years of age were invited. For once, also persons 76 years of age were invited in 2014, because the start of the program was delayed. Individuals received an invitation letter by postal mail including a single FIT (FOB-Gold; Sentinel Diagnostics, Milan, Italy). Participants with a positive FIT were referred for colonoscopy. Participants with a negative result from an FIT were reinvited 24 months after the previous invitation date. Note, this is not 24 months after a negative result from an FIT, and therefore, there screening interval could be shorter than 2 years. At the start in 2014, the cutoff for a positive test was defined at 15 μg Hb/g feces. As a result of a higher than expected participation and positivity rate and a lower than expected positive predictive value for CRC and advanced adenomas (AAs), it was decided to increase the cutoff in June 2014 to 47 μg Hb/g feces. A more extensive description of the Dutch national CRC screening program and the decision analysis on increasing the cutoff was given in a previous publication.[7] This current study evaluated the interval CRCs of participants invited in the first year of the national Dutch CRC screening program in 2014.

Outcomes

We estimated the cumulative incidence of interval cancers and test sensitivity. The cumulative incidence was calculated as the number of interval CRCs within 2 years after a negative result for an FIT in the first screening round divided by the total number of individuals with a negative result from an FIT in the first screening round. Number was presented per 10,000 individuals with a negative result from an FIT. FIT sensitivity was approximated by the number of screen-detected CRCs after a positive FIT in the first screening round divided by the sum of screen-detected and interval CRCs in the first screening round. This is a commonly applied approximation in screening literature.

We defined FIT interval CRCs according to the internationally recommended nomenclature of the working group on interval CRC of the World Endoscopy Organization.[9] They designated an interval CRC as a CRC after a negative result from an FIT but before the invitation of subsequent screening round with FIT.

An interval CRC in this study population was defined as follows for 2 distinct subgroups: (1) participants with a negative result from an FIT in 2014 and eligible for screening in the subsequent round: CRCs that occur between date of FIT analyses with negative result from an FIT and date of invitation of the subsequent screening round; and (2) participants with a negative result from an FIT in 2014 and not eligible for screening in the subsequent round because of the upper age limit: CRCs that occur between date of FIT analyses with negative FIT plus 24 months.

Screen-detected CRCs were defined as cancers detected within 6 months after a positive FIT in the first screening round.

Data Collection

Data of participants with a negative result from an FIT in 2014 were obtained from the national screening database (ScreenIT); Hb concentration, gender, age, invitation date, and date of analysis. All individual records of these participants were sent to the Netherlands Cancer Registry. This registry contained information on cancers detected in the Netherlands including data on patients, tumor, and treatment characteristics, collected from medical records. Linkage of participants with a negative result from an FIT from the screening database and the cancer registry was established by matching on initials, birth name, family name, gender, date of birth, postal code, place of birth, and date of death. If an individual with a negative result from an FIT had a CRC registered in the Netherlands Cancer Registry after the date of the FIT analyses in 2014 and before the invitation date of the second screening round, incidence date, and stage (TNM classification) were collected through the registry. To calculate the number of screen-detected CRCs, individuals with a positive FIT in 2014 were similarly linked with the Netherlands Cancer Registry and equivalent data on screen-detected CRCs were collected. All CRCs detected within 6 months after a positive FIT were considered a screen-detected CRC. For staging of CRCs, the seventh edition of the TNM classification was used. Carcinomas in situ were excluded from the analyses, because these are not invasive cancers. If individuals had more than 1 CRC diagnosed, for example at 2 different locations, the CRC with most advanced disease stage was selected for the analyses. The International Classification of Diseases for Oncology was used for coding location and was defined as rectum, rectosigmoid, sigmoid, descending colon, splenic flexure, transverse colon, hepatic flexure, ascending colon, and cecum (C18-C20).[4] Left-sided colorectal cancers included locations from rectosigmoid until descending colon and right-sided colon cancers included locations from splenic flexure to cecum. Appendiceal cancers were not considered a CRC in the Dutch CRC screening program.

Analysis

In all analyses the cutoff of 15 μg Hb/g feces was referred to as low cutoff, the cutoff of 47 μg Hb/g feces was referred to as higher cutoff. Proportions of cumulative incidence and sensitivity with 95% confidence intervals (CIs) were determined by descriptive analyses. The different subgroups (age and gender) were compared using the chi-square test. Because of a substantially different age distribution between the 2 cutoff groups, we could not use the chi-square test to compare rates by cutoff. Instead, we used the direct age standardization procedure to obtain age-adjusted rates and multivariable logistic regression analyses to test for statistically significant differences ($P < .05$) between the 2 cutoffs, adjusting for gender and age.

To also facilitate estimates for countries considering different cutoffs than 15 or 47 μg Hb/g feces, we performed an exploratory analysis to estimate the number of interval CRCs at alternative cutoffs. For every individual we used the absolute concentration of Hb in the sample to determine the numbers of individuals with an FIT positive and negative results at cutoffs of >0 μg, 10 μg, 20 μg, 40 μg, 60 μg, 80 μg, 100 μg, 120 μg, 140 μg, and 160 μg Hb/g feces and subsequently we determined how many CRCs would have been missed at those alternative cutoffs. This analysis was based on assumption that all screen-detected CRCs would have become an interval cancer when a cutoff below the measured fecal Hb concentration was applied. Vice versa we assumed that interval CRC after a negative result from an FIT of a certain fecal Hb concentration would have been detected by screening when that concentration was surpassed by the cutoff.

Data analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

In the first screening round in 2014, a total of 525,916 individuals had an assessable stool sample, of whom 40,942 (7.8%) had a positive FIT and 484,974 (92.2%) had a negative result from an FIT. A total of 127,411 individuals were assessed with the low cutoff; 15,611 (12.3%) had a positive FIT and 111,800 (87.7%) had a negative result from FIT. A total of 398,505 individuals were assessed with the higher cutoff: 25,331 (6.4%) had a positive FIT and 373,174 (93.6%) had a negative result from an FIT. A total of 33,298 (81.3%) of the FIT positive individuals had a colonoscopy follow-up. Among those with a colonoscopy follow-up, 3210 screen-

detected CRCs were diagnosed, 1102 with a low cutoff and 2108 with a high cutoff (Table 1). Among those with a negative result from an FIT, 544 interval CRCs were detected, 126 interval CRCs using the low cutoff and 418 interval CRC using the higher cutoff. Mean age of individuals tested at the low cutoff was 72.0 years and at the higher cutoff was 66.7 years. Median follow-up time between negative result from an FIT and end of interval (invitation subsequent screening round of 24 months for those over 75 years of age) was 730 (interquartile range, 726–730) days. Median follow-up time between negative result from an FIT and date of interval CRC was 469 (interquartile range, 283–618) days. Of all interval CRCs, 188 (34.6%) were detected in the first year after a negative result from an FIT and 356 (64.4%) were detected in the second year after a negative result from an FIT.

Table 1. Characteristics of the Study Population, by Cutoff

	15 μg Hb/g Feces (n = 127,411)	47 μg Hb/g Feces (n = 398,505)	Total (N = 525,916)
Gender			
Male	60,936 (47.8)	194,537 (48.8)	255,473 (48.6)
Female	66,475 (52.2)	203.968 (51.2)	270,443 (51.4)
Age			
76 *y*	54,961 (43.1)	19,256 (4.8)	74,217 (14.1)
75 *y*	25,997 (20.4)	52,204 (13.1)	78,201 (14.9)
67 *y*	16,103 (12.6)	124,768 (31.1)	140,871 (26.8)
65 *y*	28,111 (22.1)	88,340 (22.2)	116,451 (22.1)
63 *y*	2239 (1.8)	86,959 (21.8)	89,198 (17.0)
60 *y*	—	26,978 (6.8)	26,978 (5.1)
FIT negative	111,800 (87.7)	373,174 (93.69)	484,974 (92.2)
FIT positive[a]	15,611 (12.3)	25,331 (6.4)	40,942 (7.8)
Screen-detected CRCs	1102 (0.9)	2108 (0.5)	3210 (0.6)
Interval CRCs	126 (0.1)	418 (0.1)	544 (0.1)

Values are n (%).
CRC, colorectal cancer; FIT, fecal immunochemical testing.
[a]Defined as a value at or above the cutoff of 15 or 47 μg Hb/g feces.

Cumulative Incidence

The cumulative incidence of interval CRC after a negative result from an FIT in the first screening round was 11.2 (95% CI, 10.3–12.2) per 10,000 individuals (Table 2). The cumulative incidence for men of 12.2 (95% CI, 10.9–13.7) per 10,000 individuals was slightly higher than the cumulative incidence for women of 10.3 (95% CI, 9.2–11.6) per 10,000 individuals, but just not significantly different ($p = .06$). Cumulative incidence significantly increased with age (Figure 1) ($p < .001$). Note, only selected age groups were invited. After adjusting for age differences, the cumulative incidence of interval CRCs was 9.5 per 10,000 individuals at the low cutoff vs 13.8 per 10,000 individuals at the higher cutoff. Multivariable logistic regression analysis showed a significant difference between the 2 cutoffs, after adjusting for gender and age ($p = .0005$).

Sensitivity

Average sensitivity for CRC over both cutoffs in the first screening round was 85.5% (95% CI, 84.3%–86.6%). The sensitivity of 87.4% (95% CI, 86.0%–88.7%) among men was higher than the sensitivity of 82.6% (95% CI, 80.6%–84.5%) among women ($p < .001$). Sensitivity was not significantly different by age (Figure 2) ($p = .52$). Age-adjusted sensitivity at the low cutoff was 90.5% and 82.9% at the higher cutoff. Multivariable logistic regression analysis showed a significant difference between the 2 cutoffs, after adjusting for gender and age ($p < .0001$).

Exploratory analysis across the full range of relevant cutoffs showed the expected inverse correlation between cutoff and interval CRC rate, with a marked increase in interval CRC rate at high cutoffs (Figure 3). Largest decrease (1.3%–0.5%) in positivity rate was observed at low cutoffs (above 0 up to 80 μg Hb/g feces). Above 80 μg Hb/g feces, an approximately 0.3% decrease in positivity rate was observed per 10 μg Hb/g feces increase of FIT cutoff. Contrary, largest decrease in FIT sensitivity for CRC was observed at high cutoffs. FIT sensitivity drops below 70% with cutoffs higher than 90 μg Hb/g feces, with a sensitivity of only 52.0% at the FIT cutoff 160 μg Hb/g feces.

Stage Distribution and Location

A total of 93 (19.8%) stage I, 82 (17.5%) stage II, 175 (37.2%) stage III, and 120 (25.5%) stage IV interval CRCs were detected. For 74 (15.7%) interval CRCs, stage was unknown. There was no difference between the low cutoff with 75 (63.0%) interval CRCs and the high cutoff with 220 (62.7%) interval CRCs in a late stage (stage III and IV; $p = .84$). A total of 269 (52.5%) of the interval CRCs were located on the right side, 106 (20.5%) were located on the left side, and 141 (27.3%) were located at the rectum. At the low cutoff, a larger proportion of the interval CRCs (119 [57.1%]) were detected on the right-side compared with the higher cutoff (397 [50.6%]) ($p = .92$)

Discussion

In the first screening round of a national FIT-based CRC screening program, a low incidence of interval CRC in the 2 years after a negative result from an FIT was observed, irrespective of cutoff. This supports the high FIT sensitivity for CRC. However, the cumulative incidence of interval CRC was higher and sensitivity was lower for individuals tested with the higher cutoff. Older age was associated with a higher interval CRC incidence and FIT sensitivity was lower for women than for men.

Table 2. Screen-Detected and Interval Cancers, Cumulative Incidence and Sensitivity Using 2 Cutoffs

	Negative FITs	Screen-detected CRCs	Interval CRCs	Cumulative incidence per 10,000 individuals (95% CI)[a]	Sensitivity (95% CI) (%)[b]
Total					
All	484,974	3200	544	11.2 (10.3–12.2)	85.5 (84.3–86.6)
Men	231,138	1964	282	12.2 (10.9–13.7)	87.4 (86.0–88.7)
Women	253,836	1246	262	10.3 (9.2–11.6)	82.6 (80.6–84.5)
Cutoff 15 μg Hb/g feces					
All	111,800	1102	126	11.3 (9.5–13.4)	89.7 (87.9–91.3)
Age adjusted				9.5	90.5
Men	52,025	656	73	14.0 (11.1–17.7)	90.0 (87.6–92.0)
Women	59,775	446	53	8.9 (6.8–11.6)	89.4 (86.4–91.8)
Cutoff 47 μg Hb/g feces					
All	373,174	2108	418	11.2 (10.2–12.3)	83.5 (82.0–84.9)
Age adjusted				13.8	82.9
Men	179,113	1308	209	11.7 (10.2–13.4)	86.2 (84.4–87.9)
Women	194,061	800	209	10.8 (9.4–12.3)	79.3 (76.7–81.7)

CI, confidence interval; CRC, colorectal cancer; FIT, fecal immunochemical testing.
[a]Cumulative incidence is the number of interval CRCs after a negative FIT per 10,000 individuals with a negative FIT.
[b]Sensitivity is the number of screen-detected CRCs after a positive FIT divided by the total number of CRCs (screen-detected CRCs and interval CRCs).

We observed a low cumulative incidence of interval CRCs because of a high FIT sensitivity for CRC. Our estimated risk of CRC diagnosis after a negative result from an FIT is approximately 5-fold lower compared with the risk in a similar population before the introduction of CRC screening.[10] The sensitivity in the first screening round for both cutoffs (90.5% and 82.9%) was higher than anticipated (77%), based on the Dutch pilot studies preceding the national program.[6] There are 3 potential explanations for this. First, the stability of the buffer of the FIT has been improved, Consequently, higher FIT cutoffs result in similar sensitivity for CRC as lower FIT cutoffs in the past. Second, the median interval between screening rounds was longer in the pilot study (2.4 years) compared with our study (2.0 years).[6] A longer interval could result in more interval CRCs and therefore may have decreased the sensitivity. However, the third, and most important, explanation is that we estimated the sensitivity in the first screening round of the national program, which is a prevalent screening round, while the sensitivity of the pilot study was derived from the total of 3 screening rounds. In the first screening round, relatively more screen-detected CRCs will be detected than in subsequent screening rounds, but the interval CRCs will remain stable; therefore, the sensitivity is likely to decrease in subsequent screening rounds. We approximated the FIT sensitivity using screen-detected and interval CRCs, because the real

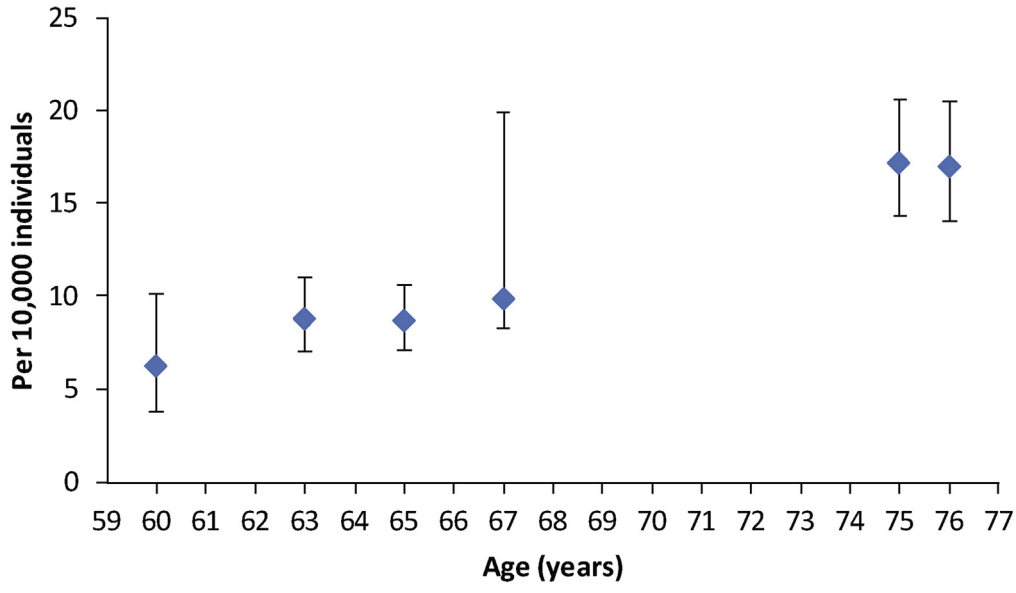

Figure 1. Cumulative incidence (number of interval colorectal cancers after a negative fecal immunochemical testing [FIT] per 10,000 individuals with a negative FIT) of interval colorectal cancer with 95% confidence interval after negative FIT.

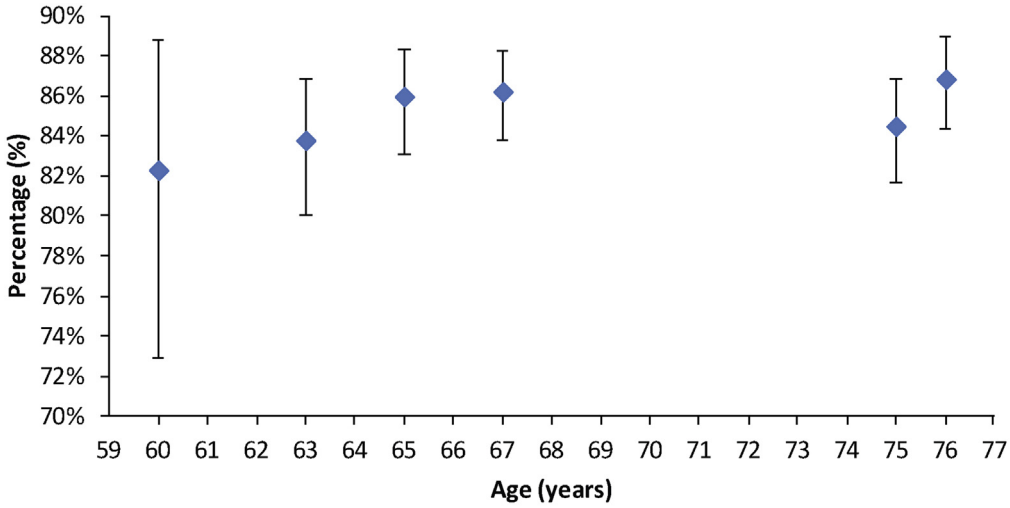

Figure 2. Fecal immunochemical testing sensitivity (number of screen-detected colorectal cancers [CRCs] after a positive fecal immunochemical testing divided by the total number of CRCs [screen-detected CRCs and interval CRCs]) with 95% confidence interval for colorectal cancer.

number of CRCs in the population at the moment of screening is unknown. This approximation has 3 biases. First, sensitivity may be overestimated, because not all missed CRCs will have developed into interval CRCs within 2 years. This hypothesis is in line with a recent systematic review, with all individuals having a colonoscopy follow-up after 1-time only FIT, showing an FIT sensitivity for CRC of 71%.[4] Second, some interval CRCs included in the definition of the sensitivity may not have been a missed screen-detected CRC, but still an AA at previous screening. This might lead to an underestimation of the sensitivity. Third, deaths before the end of the interval may have resulted in an overestimation of the sensitivity.

Our estimated FIT sensitivities are at the higher end of those observed in literature.[11–14] However, the Kaiser Permanente group also reported a sensitivity of 85% in the first screening round and then showed a decrease in sensitivity of 6%–8% in subsequent screening rounds. Consequently, the sensitivity over 4 screening rounds was approximately 80%.[11] It is therefore expected that our sensitivity will also decrease in subsequent screening rounds, and will not be that different from the 77% reported in the Dutch pilot studies.[6]

We observed differences between the age-adjusted cumulative incidence and sensitivity between the low and higher FIT cutoffs. Despite this difference, the cumulative incidence with the higher cutoff was still low, with 13.8 per 10,000 individuals, and more than 4 of 5 CRCs will be detected in the first screening round. Also, our a priori expectation was that with a higher cutoff the sensitivity would decrease with 12%. However, the observed decrease of 7.6% in this study was surprisingly smaller.[8] The exploratory analysis across the full range of relevant cutoffs showed an increase in interval CRC rate at high FIT cutoffs, which is in line with our main finding. With high FIT cutoffs (≥160 μg Hb/g feces) half of the CRCs will probably be missed.

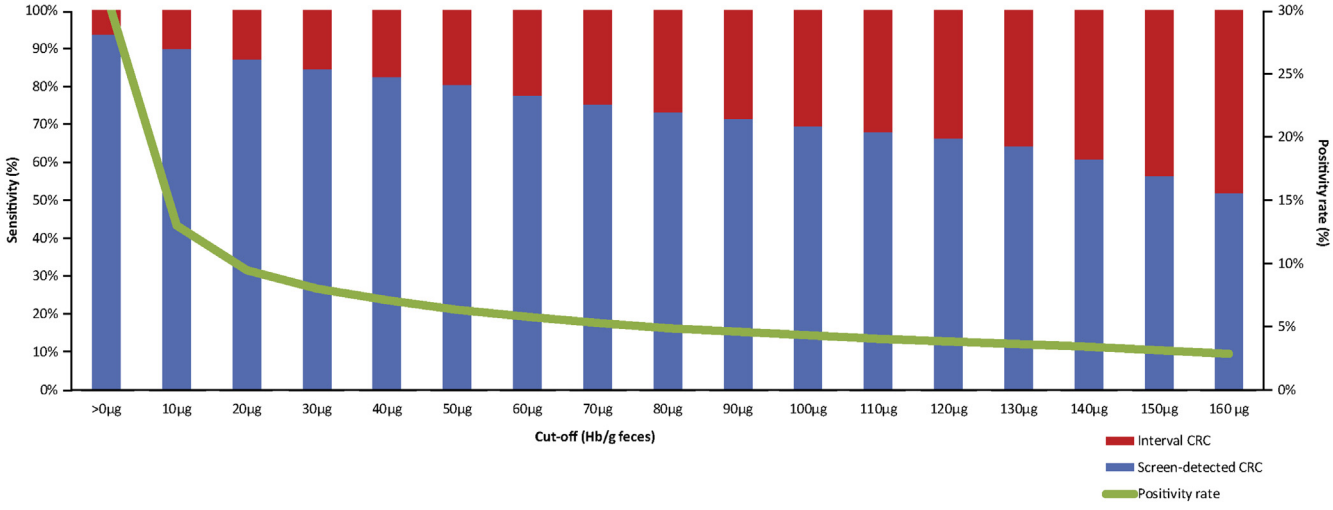

Figure 3. Positivity rate (defined as the number of participants with a test result at or above the cutoff divided by the number of participants with an assessable stool sample) and fecal immunochemical testing sensitivity (number of screen-detected colorectal cancers [CRCs] after a positive fecal immunochemical testing divided by the total number of CRCs [screen-detected CRCs and interval CRCs]) for colorectal cancer at a range of cutoffs

The sensitivity for CRC with the higher cutoff was in line with findings of the aforementioned Dutch pilot studies using a cutoff of 10 μg Hb/g feces and the Kaiser Permanente group using a cutoff of 20 μg Hb/g feces.[6,11] Again, this confirms that the performance of FIT with the old buffer using a low cutoff is comparable to the FIT, with the new buffer using a higher cutoff. In a recent systematic review, no difference in sensitivity was observed between different cutoffs, but most included studies used a relatively low cutoff (10–20 μg Hb/g feces). Nevertheless, the high sensitivity for CRC with a higher cutoff in the current study is promising for many organized programs using high FIT cutoffs.[15] The results of this study were based on FOB-Gold screening, but we do expect that they will be generalizable to other FIT brands as a recent study showed comparable performance of FOB-Gold and OC-Senso (Eiken, Japan).[16] Noteworthy is the difference between the results of the higher cutoffs with FIT in this study compared with sensitivity of guaiac fecal occult blood testing of 67.1%.[17]

Our results confirm the higher FIT sensitivity for men than for women.[6,13,14,18] This might raise the question whether different screening strategies for men and women should be applied. However, a decision analysis has shown that risk stratification by gender is currently not effective.[19] We were unable to demonstrate that FIT sensitivity differed by age. This is contrary to other findings suggesting a different sensitivity by age, although the studies presented conflicting results. The increased cumulative incidence for an interval CRC by age can be explained by the higher risk of having a CRC or AA at older age.[13,14,20,21] The stage distribution and location of the interval CRCs were similar for both cutoffs. Interestingly, the stage distribution of interval CRCs is comparable to the stage distribution of clinically detected CRCs, indicating that there probably is no false reassurance after receiving a negative result from an FIT. In contrast, location of the interval CRC is substantially different from that of CRCs detected after symptoms, with many more right-sided interval CRCs, suggesting a lower FIT sensitivity for right-sided CRCs.[22]

The major strength of this study is the opportunity of comparing 2 FIT cutoffs, applied in the same population within an organized CRC screening program. We obtained valuable information on the impact of using a higher cutoff. Another strength is the large sample size, using data of a national screening program. A limitation of the study is that we could not estimate sensitivity for AAs. AAs are mostly asymptomatic and therefore not picked up between screenings, and even then not registered at the cancer registry. A recent systematic review showed lower FIT sensitivity for AA than for CRC for 1-time testing only.[4,5] However, we expect that missed AAs will be detected with repeated FIT in subsequent screening rounds, as AAs or an early CRC. Another limitation is that the current conclusions can only be based on the results of selected age groups, due to a phased implementation by birth cohort. Now that the full screening program has been implemented, we will assess interval CRCs of all age groups and interval CRCs of subsequent screening rounds.

In conclusion, the incidence of interval CRC after a negative result from FIT is low. Although FIT sensitivity for CRC declined with a higher cutoff, it remained above 80%.

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Conflicts of interest
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