Incidence of interval colorectal cancer after negative result from first-round faecal immunochemical screening tests, by cutoff value and participant sex and age

Esther Toes-Zoutendijk, Arthur I. Kooyker, Evelien Dekker, Manon C.W. Spaander, Annemieke W.J. Opstal-van Winden, Christian Ramakers, Maaike Buskermolen, Anneke J. van Vuuren, Ernst J. Kuipers, Folkert J. van Kemenade, Marie-Louise F. Velthuysen, Maarten G.J. Thomeer, Harriët van Veldhuizen, Marjolein van Ballegooijen, Iris D. Nagtegaal, Harry J. de Koning, Monique E. van Leerdam*, Iris Lansdorp-Vogelaar*, on behalf of the Dutch national colorectal cancer screening working group.

** both authors contributed equally*

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ABSTRACT

Background

This study evaluated the interval cancer incidence after the first screening round in an organised colorectal cancer (CRC) screening programme using the FOB-Gold faecal immunochemical test (FIT) in relation to FIT cut-off.

Methods

Screening participants with a negative FIT in the first screening round in national population-based CRC screening programme in the Netherlands in 2014 were included in the study. Cumulative incidence of interval cancer after negative FIT and FIT sensitivity for CRC at a low (15 µg Hb/g faeces) and higher (47 µg Hb/g faeces) cut-off were estimated.

Results

Among the 485,112 participants with a negative FIT in 2014, 544 interval cancers were detected: 126 interval cancers among 111,800 FIT negatives at low cut-off and 418 interval cancers among 373,312 FIT negatives at higher cut-off. Mean age of individuals tested at the low cut-off was 72.0 years and at the higher cut-off was 66.7 years. The age-adjusted two-year cumulative incidences of interval cancer after negative FIT were 9.5 vs 13.8 per 10,000 persons at respectively the low cut-off and higher cut-off, which were statistically different (p 0.005). Age-adjusted FIT sensitivities for CRC were statistically different with 90.5% respectively 82.9% at the low and higher cut-off (p <0.0001). The overall FIT sensitivity for CRC was 87.4% among men and 82.6% among women (p <0.001).

Conclusions

The incidence of interval CRC after a negative FIT is low. Although FIT sensitivity for declined with a higher cut-off, it remained above 80%.

INTRODUCTION

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

FIT has been shown to be effective in detecting CRC at low cut-offs or short screening intervals.[5,6] Modelling 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 cancers in the Dutch CRC screening pilot study was recently evaluated, based on three biennial FIT screening rounds. This relatively small study showed an interval CRC incidence rate of 0.1% and a sensitivity of 77% over three screening rounds.[6] However, these interval CRCs were observed while using a very low FIT cut-off of 10 µg Hb/g faeces. In many regional or national population-based organised programmes a higher cut-off 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 programme, the FIT cut-off was increased from 15 to 47 µg Hb/g faeces, because of a higher than expected positivity rate with an associated lower positive predictive value and shortage in colonoscopy capacity.[7] Consequently, we assumed that 12% of the CRCs would be missed.[8]

Evaluation of the number of interval CRCs within organised population-based screening programmes is important. The results of the Dutch CRC FIT-based screening programme enable us to evaluate the number of interval CRCs after the first screening and determine the impact of using a relatively high versus a low FIT cut-off on the cumulative incidence and sensitivity of FIT for CRC.

METHODS

Screening programme and population

In the Netherlands a national population-based CRC screening programme was implemented in 2014, with biennial FIT screening for persons aged 55 through 75 years. The programme was rolled-out in 5 years (2014-2018), with a phased-implementation by age groups (birth cohorts). In 2014 individuals aged 60, 63, 65, 67, 75, and 76 years old were invited. For once also persons aged 76 years were invited in 2014, because the start of the programme was delayed. Individuals received an invitation letter by postal mail including one single FIT

(FOB-gold, Sentinel, Italy). Participants with a positive FIT were referred for colonoscopy. Participants with a negative FIT were re-invited 24 months after the previous invitation date. Note, this is not 24 months after a negative FIT, therefore screening interval could be shorter than 2 years. At the start in 2014, the cut-off for a positive test was defined at 15 µg Hb/g faeces. 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 (AA), it was decided to increase the cut-off in June 2014 to 47 µg Hb/g faeces. A more extensive description of the Dutch national CRC screening programme and the decision analysis on increasing the cut-off was given in a previous publication.[7] This current paper evaluated the interval CRCs of participants invited in the first year of the national Dutch CRC screening programme 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 two years after a negative FIT in the first screening round divided by the total number of individuals with a negative FIT in the first screening round. Number was presented per 10,000 individuals with a negative 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 FIT but before the invitation of subsequent screening round with FIT.

An interval CRC in this study population was defined as follows for two distinct subgroups:

1) *Participants with a negative FIT in 2014 and eligible for screening in the subsequent round*: CRCs that occur between date of FIT analyses with negative FIT and date of invitation of the subsequent screening round.
2) *Participants with a negative 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 FIT in 2014 were obtained from the national screening database ScreenIT; Hb concentration, gender, age, invitation date, and date of analyses. All individual records of these participants were sent to the Netherlands Cancer Registry (NCR). This registry contained information on cancers detected in the Netherlands including data on patients, tumour, and treatment characteristics, collected from medical records. Linkage of participants

with a negative 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 FIT had a CRC registered in the NCR 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 NKR 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 7th edition of the TNM classification was used. Tis (carcinoma in situ) were excluded from the analyses, because these are not invasive cancers. If individuals had more than one CRC diagnosed, for example at two different locations, the CRC with most advanced disease stage was selected for the analyses. The International Classification of Disease for Oncology (ICD-O) 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. Appendicael cancers were not considered a CRC in the Dutch CRC screening programme.

Analyses

In all analyses the cut-off of 15 µg Hb/g faeces was referred to as low cut-off, the cut-off of 47 µg Hb/g faeces was referred to as higher cut-off. Proportions of cumulative incidence and sensitivity with 95% confidence intervals (95% CI) were determined by descriptive analyses. The different subgroups (age and sex) were compared using chi-squared test. Because of a substantially different age distribution between the two cut-off groups, we could not use the chi-square test to compare rates by cut-off. Instead, we used multivariable logistic regression analyses to test for statistically significant differences (p <0.05) between the two cut-offs, adjusting for gender and age.

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

Data analyses were performed using R version 3.5.0.

RESULTS

In the first screening round in 2014, a total of 525,916 individuals had an assessable stool sample, of which 40,942 (7.8%) had a positive FIT and 484,974 (92.2%) had a negative FIT. 127,411 were assessed with the low cut-off; 15,611 (12.3%) had a positive FIT and 111,800 (87.7%) had a negative FIT. 398,505 were assessed with the higher cut-off;25,331 (6.4%) had a positive FIT and 373,174 (93.6%) had a negative FIT. 33,298 (81.3%) of the FIT positives had a colonoscopy follow-up. Among those with a colonoscopy follow-up, 3,210 screen-detected CRCs were diagnosed, 1,102 with a low cut-off and 2,108 with a high cut-off (Table 1). Among those with a negative FIT, 544 interval CRCs were detected: 126 interval CRCs with the low cut-off and 418 interval CRCs with the higher cut-off. Mean age of individuals tested at the low cut-off was 72.0 years and at the higher cut-off was 66.7 years. Median follow-up time between negative FIT and end of interval (invitation subsequent screening round of 24 months for those over 75 years of age) was 730 (IQR 726-730) days. Median follow-up time between negative FIT and date of interval CRC was 469 (IQR 283-618) days. Of all interval CRCs, 188 (34.6%) were detected in the first year after a negative FIT, and 356 (64.4%) were detected in the second year after a negative FIT.

Table 1: Characteristics of the study population by cut-offs (15 and 47 µg Hb/g faeces)

	15 µg	47 µg	Total
	n (%)	n (%)	n (%)
Total tested	127,411 (100)	398,505 (100)	525,916 (100)
Gender			
Men	60,936 (47.8)	194,537 (48.8)	255,473 (48.6)
Women	66,475 52.2)	203,968 (51.2)	270,443 (51.4)
Age			
76	54,961 (43.1)	19,256 (4.8)	74,217 (14.1)
75	25,997 (20.4)	52,204 (13.1)	78,201 (14.9)
67	16,103 (12.6)	124,768 (31.1)	140,871 (26.8)
65	28,111 (22.1)	88,340 (22.2)	116,451 (22.1)
63	2,239 (1.8)	86,959 (21.8)	89,198 (17.0)
60	-	26,978 (6.8)	26,978 (5.1)
FIT Negative	111,800 (87.7)	373,174 (93.69)	484,974 (92.2)
FIT Positive*	15,611 (12.3)	25,331 (6.4)	40,942 (7.8)
Screen-detected CRCs	1,102 (0.9)	2,108 (0.5)	3,210 (0.6)
Interval CRCs	126 (0.1)	418 (0.1)	544 (0.1)

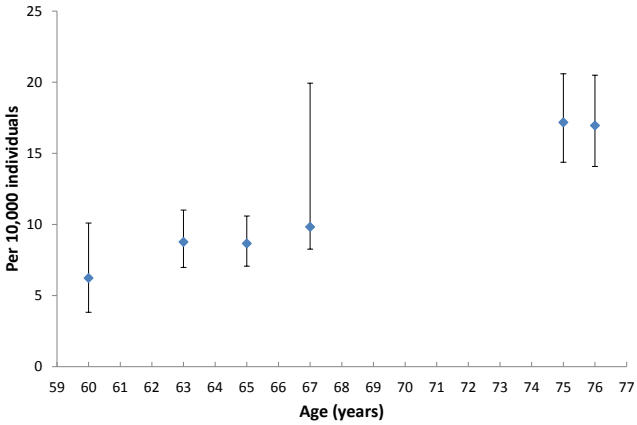
Abbreviations: CRC (colorectal cancer), FIT (faecal immunochemical testing)

*Positive test was defined as a value at or above the cut-off of 15 or 47 µg Hb/g faeces.

Cumulative incidence

The cumulative incidence of interval CRC after a negative FIT in the first screening round was 11.2 (95%CI: 10.3-12.2) per 10,000 individuals. 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 0.06). Cumulative incidence significantly increased with age (Figure 1; p <0.001). 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 cut-off vs 13.8 per 10,000 individuals at the higher cut-off. Multivariable logistic regression analysis showed a significant difference between the two cut-offs, after adjusting for gender and age (p 0.0005).

Figure 1: Cumulative incidence* of interval colorectal cancer with 95% confidence interval after negative FIT



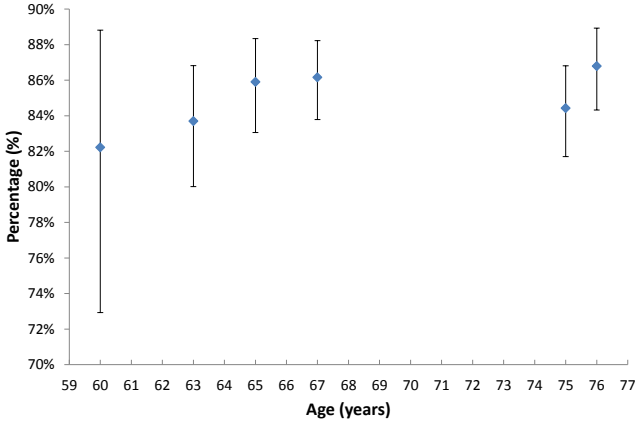
Abbreviations: FIT (faecal immunochemical testing)
*Cumulative incidence is the number of interval CRCs after a negative FIT per 10,000 individuals with a negative FIT.

Sensitivity

Average sensitivity for CRC over both cut-offs 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 <0.0001). Sensitivity was not significantly different by age (Figure 2; p 0.52). Age-adjusted sensitivity at the low cut-off was 90.5% and 82.9% at the higher cut-off. Multivariable logistic regression analysis showed a significant difference between the two cut-offs, after adjusting for gender and age (p <0.0001).

Exploratory analysis across the full range of relevant cut-offs showed the expected inverse correlation between cut-off and interval CRC rate, with a marked increase in interval CRC rate at high cut-offs (Figure 3). Largest decrease (1.3-0.5%) in positivity rate was observed at low cut-offs (above 0 up to 80 µg Hb/g faeces). Above 80 µg Hb/g faeces approximately

Figure 2: FIT sensitivity with 95% confidence interval for colorectal cancer



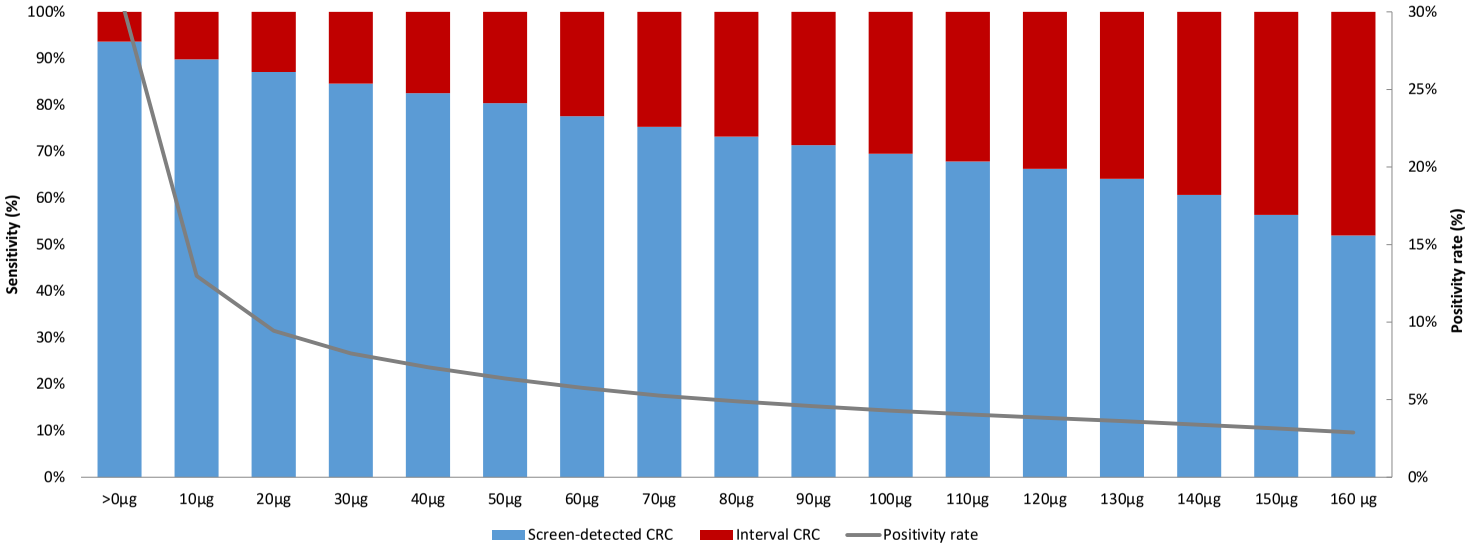
Abbreviations: FIT (faecal immunochemical testing)
*Sensitivity is the number of screen-detected CRCs after a positive FIT divided by the total number of CRCs (screen-detected CRCs and interval CRCs).

0.3% decrease in positivity rate was observed per 10 µg Hb/g faeces increase of FIT cut-off. Contrary, largest decrease in FIT sensitivity for CRC was observed at high cut-offs. FIT sensitivity drops below 70% with cut-offs higher than 90 µg Hb/g faeces, with a sensitivity of only 52.0% at the FIT cut-off 160 µg Hb/g faeces.

Stage distribution and location

A total of 93 (19.8%) stage I interval CRCs were detected, 82 (17.5%) stage II interval, 175 (37.2%) stage III interval CRCs and 120 (25.5%) stage IV interval CRCs. Of 74 (15.7%) interval CRCs stage was unknown. There was no difference between the low cut-off with 75 (63.0%) interval CRCs and the high cut-off with 220 (62.7%) interval CRCs in a late stage (stage III and IV, *p* 0.84) 269 (52.5%) of the interval CRC were located right-sided, 106 (20.5%) left-sided and 141 (27.3%) at the rectum. At the low cut-off a larger proportion of the interval CRCs (119 (57.1%)) was detected right-sided compared to the higher cut-off (397 (50.6%), *p* 0.92)

Figure 3: Positivity rate* and FIT sensitivity† for colorectal cancer at a range of cut-offs



Abbreviations: FIT (faecal immunochemical testing)

*Positivity rate was defined as the number of participants with a test result at or above the cut-off divided by the number of participants with an assessable stool sample.

†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).

Table 2: Screen-detected and interval cancers, cumulative incidence and sensitivity using two cut-offs (15 and 47 µg Hb/g faeces)

	Cut-off Hb/g faeces	Negative FITs	Screen-detected CRCs	Interval CRCs	Cumulative incidence*	Sensitivity†
	Total	n	n	n	Per 10,000 individuals (95% CI)	% (95% CI)
All		484,974	3,200	544	11.2 (10.3-12.2)	85.5 (84.3-86.6)
Men		231,138	1,964	282	12.2 (10.9-13.7)	87.4 (86.0-88.7)
Women		253,836	1,246	262	10.3 (9.2-11.6)	82.6 (80.6-84.5)
All	15 µg	111,800	1,102	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)
All	47 µg	373,174	2,108	418	11.2 (10.2-12.3)	83.5 (82.0-84.9)
Age adjusted					*13.8*	*82.9*
Men		179,113	1,308	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)

Abbreviations: CRC (colorectal cancer), FIT (faecal immunochemical testing)

*Cumulative incidence is the number of interval CRCs after a negative FIT per 10,000 individuals with a negative FIT.

†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).

DISCUSSION

In the first screening round of a national FIT-based CRC screening programme, a low incidence of interval CRC in the two years after a negative FIT was observed, irrespective of cut-off. 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 cut-off. Older age was associated with a higher interval CRC incidence and FIT sensitivity was lower for women than for men.

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 FIT is approximately 5-fold lower compared to the risk in a similar population before the introduction of CRC screening.[10] The sensitivity in the first screening round for both cut-offs (90.5% and 82.9%) was higher than anticipated (77%), based on the Dutch pilot studies preceding the national programme.[6] There are three potential explanations for this. First, the stability of the buffer of the FIT has been improved. Consequently, higher FIT cut-offs result in similar sensitivity for CRC as lower FIT cut-offs in the past. Second, the median interval between screening rounds was longer in the pilot study (2.4 years) compared to 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 programme, which is a prevalent screening round, while the sensitivity of the pilot study was derived from the total of three 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 number of CRCs in the population at the moment of screening is unknown. This approximation has three biases. First, sensitivity may be overestimated, because not all missed CRCs will have developed into interval CRCs within two years. This hypothesis is in line with a recent systematic review with all individuals having a colonoscopy follow-up after one-time only FIT, showing a 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 four 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 cut-off. Despite this difference, the cumulative incidence with the higher cut-off was still low with 13.8 per 10,000 individuals and more than 4 out of 5 CRCs will be detected in the first screening round. Also, with our prior assumption that 12% of the CRC would be missed, we would expect a decrease in sensitivity around 10%. However, the decrease of 7.6% in this study was smaller.[8] The exploratory analysis across the full range of relevant cut-offs showed an increase in interval CRC rate at high FIT cut-offs, which is in line with our main finding. With high FIT cut-offs (>= 160 µg Hb/g faeces) half of the CRCs will probably be missed

The sensitivity for CRC with the higher cut-off was in line with findings of the aforementioned Dutch pilot studies using a cut-off of 10 µg Hb/g faeces and the Kaiser Permanente group using a cut-off of 20 µg Hb/g faeces.[6,11] Again this confirms that the performance of FIT with the old buffer using a low cut-off is comparable to the FIT with the new buffer using a higher cut-off. In a recent systematic review, no difference in sensitivity was observed between different cut-offs, but most included studies used a relatively low cut-off (10-20 µg Hb/g faeces). Nevertheless, the high sensitivity for CRC with a higher cut-off in the current study is promising for many organised programmes using high FIT cut-offs.[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-Sensor.[16] Noteworthy is the difference between the results of the higher cut-offs with FIT in this study compared to sensitivity of guaiac Faecal Occult Blood Testing (gFOBT) 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 cut-offs. 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 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 two FIT cut-offs, applied in the same population within an organised CRC screening programme. We obtained valuable information on the impact of using a higher cut-off. Another strength is the large sample size, using data of a national screening programme. A limitation of the study is that we could not estimate sensitivity for AA. 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 one-time testing only.[4,5] However, we expect that missed AA will be detected with repeated FIT in subsequent screening rounds, as AA 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 the full screening programme is 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 FIT is low. Although FIT sensitivity for declined with a higher cut-off, it remained above 80%.

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