Effects of increasing screening age and fecal hemoglobin cut-off concentration in a colorectal cancer screening program

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ABSTRACT

Background & Aims

Several countries have implemented programs to screen for colorectal cancer (CRC) using the fecal immunochemical test (FIT). These programs vary considerably in age of the population screened and the cut-off concentration of fecal hemoglobin (Hb) used to identify candidates for further evaluation; these variations are usually based a country's colonoscopy resources. We calculated how increasing the Hb cut-off concentration and screening age affects colonoscopy yield, missed lesions, and demand.

Methods

We collected data from 10,008 average-risk individuals in The Netherlands, 50–74 years old, who were invited for a FIT in the first round of a population-based CRC screening program from November 2006 through December 2008. Fecal samples were collected and levels of Hb were measured using the OC-sensor Micro analyzer; concentrations ≥10 µg Hb/g feces were considered positive. Subjects with a positive FIT were scheduled for colonoscopy within 4 weeks. Logistic regression analysis was performed to evaluate the association between age and detection of advanced neoplasia.

Results

In total, 5986 individuals (62%) participated in the study; 503 had a positive test result (8.4%). Attendance, positive test results, detection advanced neoplasia, and the FIT's positive predictive value (PPV) all increased significantly with age (P<.001). Detection of advanced neoplasia ranged from 1.3% in the youngest age group to 6.2% in the oldest group; the PPV value of the FIT was 26% in the youngest group and 47% in the oldest group. Increasing the starting age of invitees from 50–74 years to 55–74 years reduced the proportion of subjects who underwent colonoscopy evaluation by 14% and resulted in 9% more subjects with advanced neoplasia being missed. Increasing the cut-off concentration from 10 to 15 µg Hb/g feces reduced the proportion of subjects who underwent colonoscopy evaluation by 11% and resulted in 6% of advanced neoplasia being missed.

Conclusion

In an analysis of an average-risk screening population in The Netherlands, we found that detection of advanced neoplasia by FIT increases significantly with age and fecal Hb cut-off concentration. Increasing the cut-off concentration or screening age reduces the numbers of patients who undergo colonoscopy evaluation in FIT-based CRC screening programs. Our findings provide insight in these effects per age category and cut-off concentration, and the consequences, in terms of missed lesions.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality in the Western world.[1] Screening with guaiac-based fecal occult blood tests (gFOBT) can reduce CRC-related mortality.[2] The gFOBT is now gradually replaced by fecal immunochemical test (FIT) for hemoglobin because of its superior adherence and accuracy.[3] Quantitative FIT furthermore offers the opportunity of selecting a specific cut-off fecal Hb concentration used to identify candidates for further evaluation; that provides an optimal match between screening population and available financial and endoscopy resources.

In recent years, several countries have implemented a FIT-based nationwide CRC screening program.[4] Cut-off concentration and age of the population screened vary between countries, often tailored to available financial resources and colonoscopy capacity.[5, 6] For example, organized FIT screening is offered to 55-75 year-olds in the Netherlands, using a positivity cut-off of 47 µg Hb/g feces, whereas in the United Kingdom 60-74 year-olds are invited for FIT screening and a cut-off concentration of 20 µg Hb/g feces is used. A high cut-off and narrow screening age range result in a low positivity rate and consequently low colonoscopy demand.[7] However, this comes at the cost of a decrease in detection rate of advanced neoplasia (AN).[7]

Previous studies showed that the prevalence of AN, defined as colorectal cancer and advanced adenomas, increases with age in individuals undergoing a screening colonoscopy.[8, 9] Also, fecal Hb concentrations determined by FIT tend to increase with age, and higher positivity rates and detection rates are found in elder screenees compared to younger screenees.[10-12] Therefore, age partitioned cut-offs for fecal Hb concentration may be warranted if AN detection rate increases relatively slower than positivity rate.

The aim of this study was to assess positivity rates and detection rates of FIT in different age categories and to assess how this relates to the positive predictive value (PPV) in a population-based CRC screening program. Our secondary aim was to estimate the effect of increasing the cut-off concentration and screening age on the numbers of patients who undergo colonoscopy and AN detection and miss rate.

METHODS

Study population

This study compromises the first round of a population-based organized CRC screening program (CORERO-I) by means of FIT, of which the methods and primary results have been described elsewhere.[13-15] In short, 10,008 CRC screening-naïve individuals aged 50-74 years living in region Rotterdam-Rijnmond in the South-West of the Netherlands were randomly selected and invited. We excluded individuals who met one of the exclusion criteria (a history of inflammatory bowel disease or CRC; colonoscopy, sigmoidoscopy, or barium contrast enema within the previous three years; inability to give informed consent) or who died or moved away. Recruitment took place between November 2006 and December 2008.

For the purpose of this study, we assessed rates of attendance, test positivity, detection of AN, and PPV in the following five age categories; 50-54, 55-59, 60-64, 65-69 and 70-74 years. In these age groups, we also calculated differences in the diagnostic yield of FIT, number needed to screen and number needed to scope to detect one case with AN. We further assessed if the PPV differed with age, when corrected for the confounders gender, socioeconomic status and fecal Hb concentration. We calculated the effect of offering CRC screening to later ages with steps of 5 years on the numbers of patients who undergo colonoscopy and number of detected and missed AN. We also assessed the effect of increasing cut-off concentrations on these parameters. Finally, the effect of these screening strategies was converted into a risk ratio with 95% CI, i.e. the percentage reduction of those who undergo colonoscopy was divided by the percentage of missed advanced neoplasia. This ratio explains the relative decrease in colonoscopy demand per percentage lesion missed advanced neoplasia.

Intervention and follow-up evaluation

One FIT (OC-sensor, Eiken Chemical, Tokyo, Japan) was sent by mail to collect a single sample of one bowel movement. Participants returned the FIT and an informed consent form at ambient temperature by freepost to the Gastroenterology & Hepatology laboratory of the Erasmus Medical Centre, Rotterdam, the Netherlands. The test was analyzed on the OC-sensor Micro system (Eiken, Japan) and considered positive at a fecal Hb concentration of ≥10 µg Hb/g feces (≥ 50 ng Hb/mL) (Appendix 1).

Subjects with a positive FIT were scheduled for colonoscopy within four weeks and subjects with a negative FIT were referred back to the screening program. All colonoscopies were done by experienced gastroenterologists. Removed polyps were evaluated by expert gastrointestinal pathologists. Patients with a positive colonoscopy entered a surveillance program, whereas subjects with a negative colonoscopy were considered not to require FIT screening for 10 years.[16]

Definitions

Attendance rate was calculated by dividing the number of eligible participants by all eligible subjects (all invitees minus the excluded clients). Positivity rate was defined as the proportion of positive tests in participants with an analyzable test-result. Detection rate was defined as those with AN or CRC relative to all participants with an analyzable test. Advanced neoplasia included CRC and advanced adenomas. An advanced adenoma was defined as an adenoma ≥ 10 mm, with ≥ 25% villous component and/or high-grade dysplasia. When multiple lesions were present in one person, the screenee was classified according to the most advanced lesion. The PPV compromised all screenees diagnosed with AN or CRC proportionally to screenees with a positive FIT who underwent a colonoscopy. The diagnostic yield of FIT per 10,000 eligible invitees was defined as screenees with AN relative to all eligible invitees. Number needed to scope was calculated as the number of colonoscopies needed to find one screenee with AN. Number needed to screen describes the number of complete FITs needed to find one case with AN.

Statistical analyses

Comparisons of continuous variables were performed using the Mann–Whitney U-test. Categorical variables with two categories were compared using the $\chi2$ test and those with multiple categories with binary logistic regression analyses. Equality of fecal Hb concentration distributions between age categories was tested with the Kruskal-Wallis test. Attendance rate, positivity rate, detection rate and PPV were described as proportions with 95% confidence intervals (CI).

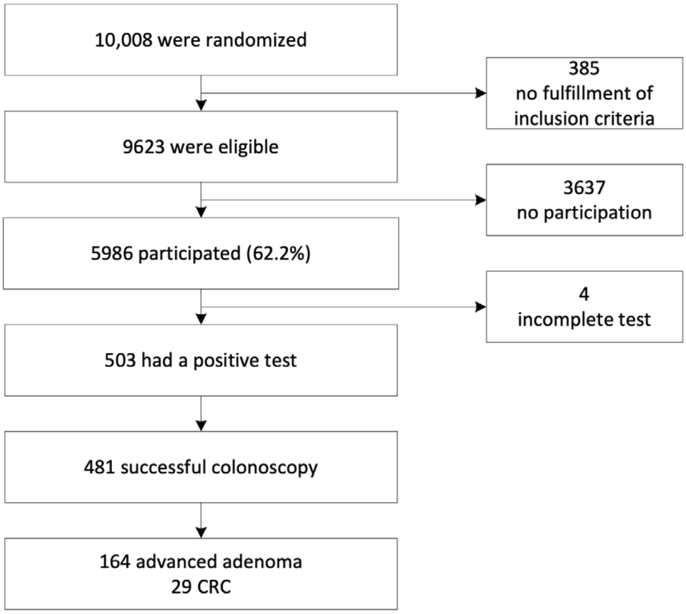
To estimate significant differences in PPV for all ages, a multivariate binary regression analysis was performed, with age included as continuous variable. First, univariate binary logistic regression analyses were performed to determine the independent association of multiple variables (sex, age, social economic status, fecal Hb concentration) with the PPV of AN. In these analyses the PPV was used as outcome variable by selecting all participants with an analyzable FIT. In addition, detection of AN was selected as the dependent variable. Subsequently, all univariate significant variables and variables chosen by the clinician's rationale (i.e. gender) were included in a multivariate logistic regression analysis. Interactions were tested between all variables that were included in the multivariate model. Interactions were included in the final model when significant ($P<0.01$). Hosmer and Lemeshow chi-square statistics were used as goodness of fit statistic. The outcome of the final multivariate logistic regression model resulted in a predicted probability of having AN per screenee who had a positive FIT and subsequent colonoscopy. These predicted probabilities of having AN per screenee were depicted in a figure with age as a continuous variable.

The analyses were performed using SPSS V.21 statistical package (SPSS Inc, Chicago, Illinois, USA). All p-values were two-sided and considered significant if $P<0.05$, except for interactions which were considered significant if $P<0.01$.

Ethical approval

All participants signed informed consent. The study was approved by the Dutch Ministry of Health (2006/02WBO). The invitation letters and information brochures were approved by the Institutional Review Board of the Erasmus MC (MEC-2005-264). All authors had access to the study data and reviewed and approved the final manuscript.

Figure 1 Trial profile



CRC: Colorectal cancer

RESULTS

Participant characteristics

The trial profile is summarized in Figure 1. Of the 10,008 individuals invited, 385 subjects were excluded from analyses, due to various reasons as described previously.[13-15] In total, 5,986 (62%) attended screening, of which 5,982 had an analyzable screening test. A total of 503 (8.4%) screenees had a positive test at a cut-off concentration of ≥10 µg Hb/g feces of which 481 (96%) underwent colonoscopy.

Test characteristics per age

Test results per age category are given in Table 1. Screening participants had a median age of 61 years and 48% of the participants was male. Attendance rate and positivity rate increased significantly with age ($P<.001$). Detection rates of AN and CRC increased significantly with age as continuous variable ($P<.001$), and ranged from 1.3% for AN in the youngest age category of 50 to 54 years old, to 6.2% in the eldest age category of 70 to 74 years. The PPV for AN per age category ranged from 26% to 47%. The number needed to screen and number needed to scope to detect one case with AN ranged from 138 to 26 and 3.9 to 2.1, respectively. The diagnostic yield of AN per 10,000 eligible invitees ranged from 73 in the 50 to 54 year-old to 392 in the 70 to 74 year-old.

Table 1 Test characteristics of FIT for five different age categories in a colorectal screening program.

Age categories	**Eligible invitees**	**Attendance rate**	**Positivity rate**	**Underwent colonoscopy**	**Detection rate**		**PPV**		**Number needed to screen to detect one person with AN**	**Number needed to scope detect one person with AN**	**Diagnostic yield of AN per 10,000**
					AN	**CRC**	**AN**	**CRC**			
years	n	n (%)	n (%)	n (%)	n (%)	n (%)	%	%			
50-54	2,343	1,343 (57)	68 (5.1)	66 (97)	17 (1.3)	1 (0.07)	25.8	1.5	138	3.9	73
55-59	2,381	1,467 (62)	106 (7.2)	99 (93)	41 (2.8)	8 (0.55)	41.4	8.1	58	2.4	172
60-64	2,149	1,419 (66)	119 (8.4)	113 (95)	41 (2.9)	5 (0.35)	36.3	4.4	52	2.8	190
65-69	1,577	1,015 (64)	110 (10.8)	106 (96)	48 (4.7)	6 (0.59)	45.3	5.7	33	2.2	304
70-74	1,173	742 (63)	100 (13.5)	97 (97)	46 (6.2)	9 (1.21)	47.4	9.3	26	2.1	392
Total	9,623	5,986 (60)	503 (8.4)	481 (96)	193 (3.2)	29 (0.50)	40.1	6.0	50	2	201

FIT: fecal immunochemical test; PPV: positive predictive value; AN: advanced neoplasia; CRC: colorectal cancer.

Test characteristics per cut-off

Fecal Hb concentration ranged from 0 to 921 µg Hb/g feces in participants with an analyzable screening test. Fecal Hb concentration increased significantly with age as a continuous variable (p<.001) and was significantly higher in men than in women (p<.001). Positivity rate decreased from 8,4% to 6,2%, 4,4% and 3,8% when the cut-off was increased from ≥10 µg Hb/g feces to sequentially ≥20 µg Hb/g feces, ≥30 µg Hb/g feces, and ≥40 µg Hb/g feces.

Regression model

Univariate logistic regression analyses showed that an increase in age (*P*=.003) and increase in fecal Hb concentration (*P*<.001) were both associated with a higher PPV (Table 2). Age remained significantly related to PPV in the multivariate logistic regression analysis, with an odds ratio (OR) of 1.53 per 10 years (95% CI 1.13-2.07), when corrected for fecal Hb concentration and gender. There were no significant interactions in this model and no significant differences in frequencies between the observed values and the predicted values (Goodness-of-Fit; *P*=.276). The predicted probability of having AN for participants with a positive FIT per age, corrected for gender and fecal Hb concentration, was depicted in Figure 2 for different fecal Hb concentration subgroups.

Table 2 Univariate and multivariate logistic regression analyses of factors associated with the detection of advanced neoplasia in a FIT based CRC screening program.

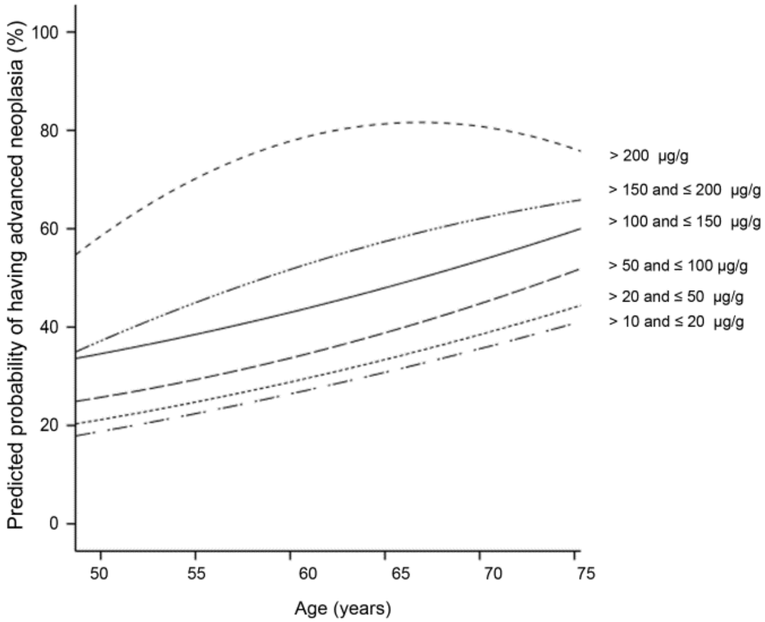
	Univariate		Multivariate	
	Odds ratio (95% CI)	**p-value**	**Odds ratio** (95% CI)	**p-value**
Sex male	1.24 (0.85-1.81)	.27	1.12 (0.74-1.68)	.60
Age (per ten years increase)	1.53 (1.15-2.03)	.003	1.53 (1.13-2.07)	.005
Socio-economic status (SES)		.43		
Low	*Reference*			
Middle	0.90 (0.54-1.48)			
High	0.76 (0.51-1.15)			
Fecal Hb concentration (per 10 µg Hb/g feces increase)	1.07 (1.05-1.09)	<.001	1.07 (1.05-1.09)	<.001

FIT: fecal immunochemical test; CRC: colorectal cancer.

Increasing the screening starting age and cut-off

Colonoscopy demand and detection rate of AN per age category and cut-off concentration are shown in Figure 3a and Figure 3b. Increasing the starting age from 50 to 55 years resulted in a total decrease in colonoscopy demand of 14%, however at the expense of missing 9% of AN (Table 3). If solely the cut-off was increased from 10 to 12,5 µg Hb/g feces, this resulted in a decreased colonoscopy demand of 11%, at the expense of missing

Figure 2 The predicted probability of having advanced neoplasia displayed for screenees with a positive FIT per age and different fecal hemoglobin concentrations* (corrected for gender)



*microgram hemoglobin per gram feces
FIT: fecal immunochemical test.

7% AN. Thus in both strategies, for every 1.6% decrease in subjectss who undergo colonoscopies, 1% of screenees with AN were missed, resulting in a 1.6 ratio.

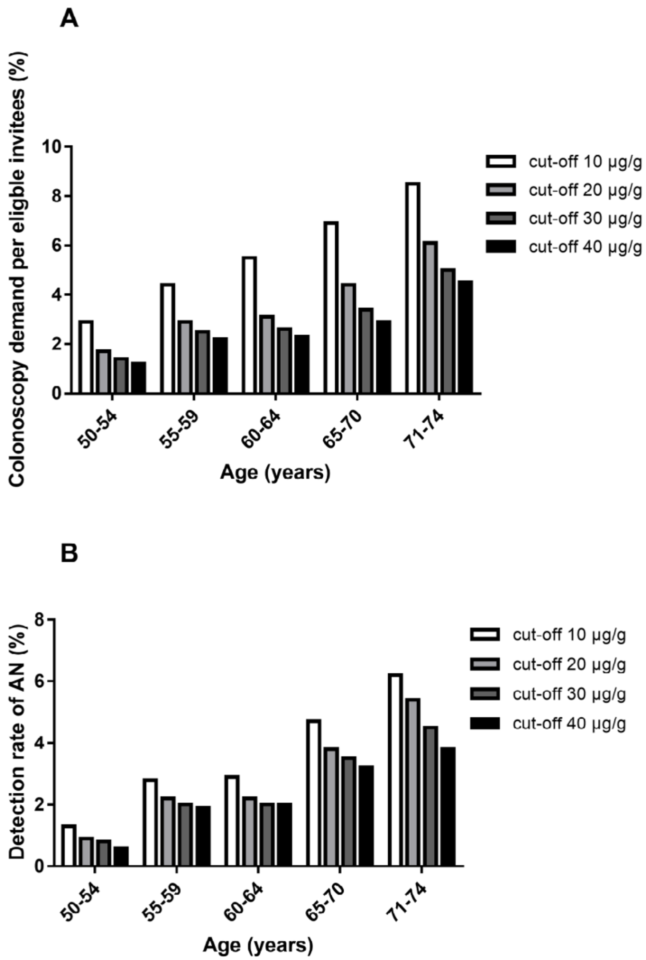
Screening strategies with age-specific cut-off concentrations were also assessed on these outcomes (Table 3). The highest benefit of the reduction of numbers of patients who undergo colonoscopy relative to the loss in AN detection was achieved by strategy 6 and, while strategy one and five resulted in the lowest decrease of AN detection rate.

Total colonoscopies needed and detected lesions are shown, compared to the reference screening strategy (first round, screen age 50-74 years, cutoff 10 µg Hb/g feces). Screening strategies are altered by 1. increasing the starting age and 2. increasing cut-offs and 3. Combinations of age and cut-off alterations FIT: fecal immunochemical test; Hb: Hemoglobin; AN: Advanced Neoplasia; CRC: colorectal cancer; µg: microgram; g: gram; PPV: positive predictive value.

DISCUSSION

In this study we showed that there were substantial differences in diagnostic yield of FIT between age groups. In this population-based CRC screening cohort, FIT positivity

Figure 3a) Colonoscopy demand and **b)** detection rate of advanced neoplasia (AN) per age category and cut-off concentration in μg Hb/gram feces.



rates, detection rates and the PPV all significantly increased with age. Both increasing the screening starting age and increasing the cut-off concentration resulted in a substantial reduction in colonoscopy demand.

Currently, cut-off concentrations and age of the population screened varies between countries with a FIT-based screening program.[4] FIT-based screening with more tailored approaches based on sex, age or risk factors have been suggested in several studies.[11, 12] We calculated the effect of increasing the screening starting age and cut-off concentration on colonoscopy demand and number of detected and missed AN. We showed that both

Table 3 Effects of FIT-based CRC screening strategies on the numbers of patients who undergo colonoscopy and missed lesions in a screening population of 10,000 eligible invitees.

Number strategy	Screening strategies	Total colonoscopies needed per 10,000 eligible invitees	Detected lesions per 10,000 eligible invitees		Ratio of percentage decrease in colonoscopies needed per percentage AN missed
	Age range, cut-off (µg Hb/g feces)	N (%*)	AN (%*)	CRC (%*)	(95% CI)
	50-74, 10 (reference)	*500*	*201*	*30*	
1	55-74, 10	431 (-14)	183 (-9)	29 (-3)	1.6 (0.94 – 2.52)
2	60-74, 10	328 (-34)	141 (-30)	21 (-30)	1.2 (0.90 – 1.47)
3	65-74, 10	211 (-58)	98 (-51)	15 (-50)	1.1 (0.97 – 1.32)
4	70-74, 10	99 (-80)	48 (-76)	9 (-70)	1.1 (0.96 – 1.15)
5	50-74, 12.5	447 (-11)	188 (-7)	28 (-7)	1.6 (0.91 – 2.93)
6	50-74, 15	374 (-25)	175 (-13)	28 (-7)	1.9 (1.32 – 2.88)
7	50-74, 20	316 (-37)	160 (-20)	28 (-7)	1.9 (1.34 – 2.43)
8	50-74, 50	202 (-60)	119 (-41)	21 (-30)	1.5 (1.21 – 1.75)
9	50-74, 100	134 (-73)	93 (-54)	16 (-47)	1.4 (1.19 – 1.57)
10	50-54, 30; 55-59, 25; 60-64, 20; 65-69, 15; 70-74, 10	347 (-31)	166 (-18)	29 (-3)	1.8 (1.23 – 2.44)
11	50-54, 10; 55-59, 15; 60-64, 20; 65-69, 25; 70-74, 30	334 (-33)	160 (-21)	27 (-10)	1.6 (1.21 – 2.20)

*percentage decrease

actions result in a substantial reduction in colonoscopy demand. However, also AN and CRC are missed subsequently. Increasing the screening starting age and increasing the cut-off concentration had different effects on the absolute numbers of screenees who undergo colonoscopy and missed lesions. An interesting finding was however that in relative ratios equal effects were found. For every missed AN in one screenee, both increasing the cut-off concentration and increasing the starting age, resulted in a similar decrease in screenees who undergo colonoscopy.

In our cohort, the PPV for AN increased significantly with age, even when corrected for confounders. This is in line with a recent Spanish study.[17] A likely explanation for the increasing PPV of FIT with age is that a greater proportion of AN occurs in elder persons.[8, 9]

Lower detection rates compared to elder individuals are generally accepted as younger persons have more life-years to gain.[18]

In addition to age, we showed that incremental increase of fecal Hb concentration detected by FIT is associated with an increase in PPV for AN, suggesting (pre)malignant lesions bleed more compared to other lesions. This mechanism is also suggested in previous literature.[17] Differences in detection rates between age groups, sex and fecal Hb concentrations determined by FIT have been described before in FIT-based CRC screening populations.[19-21] In our cohort, sex was not associated with the PPV for AN. This is most likely due to the small absolute numbers of screenees with AN in our study. Literature has shown that FIT detects AN more often in males than females.[11, 22]

The relation between fecal hemoglobin concentrations and age on the predicted probability of having AN was linearly shaped for the lower concentrations and parabolically shaped for the higher concentrations. This parabolic shape is possibly a result of the low numbers of subjects with high fecal Hb concentrations for the youngest and oldest ages. In addition, a prozone effect might have occurred at very high fecal Hb concentrations (>200 µg Hb/g feces). A prozone effect can appear if the fecal Hb concentration exceeds the limit of antigen agglutination.[23] As a result, the actual sample concentration can be higher than the measured Hb values for values >200 µg Hb/g feces. It should be of note that it is hypothesized that FIT is relatively insensitive for the detection of serrated neoplasia.[24] Serrated lesions are thought to bleed less often compared with adenomas.[25-27]

An optimal cut-off concentration or screening age range could not be established in this study. Evidence has been published that in a Western population the optimal cut-off concentration is low (10 µg Hb/g feces) and screening age range is wide (45-80 years).[18] However, such screening programs require the availability of unlimited colonoscopy resources. In our study we showed that alterations in cut-off concentrations and age of the population screened are both good options when facing colonoscopy capacity limitations, dependent on available resources.

The main limitation of our study is the size of the cohort. Since CRC was detected in only few persons, changes in the cut-off concentration or screening starting age had a substantial effect in percentage of missed CRC. Therefore, the effect of increasing the screening starting age and cut-off concentration on the missed CRCs should be carefully interpreted. However, our study size was acceptable to calculate effects of screening alterations on detected and missed AN. Information on age differences in missed lesions in population based FIT screening has been limited until now. This study provides insight into this matter. It should however be taken into account that in our cohort only those subjects with a cut-off ≥ 10 μg Hb/g feces were offered colonoscopy. Missed lesions below this cut-off could therefore not be evaluated.

In conclusion, increased age is associated with an increase in positivity rates, detection rates and PPV in a FIT-based CRC screening cohort. Our findings give insight in the effect of increasing the screening starting age and cut-off concentration on colonoscopy demand and missed lesions in absolute numbers. When facing colonoscopy capacity problems, these effects can be taken into account. Further research to evaluate the impact of age-tailored cut-offs in multiple screening rounds is needed.

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