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Research Article

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Test Performance of Immunologic Fecal Occult Blood Testing and Sigmoidoscopy Compared with Primary Colonoscopy Screening for Colorectal Advanced Adenomas

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Abstract

Given the current increase in colorectal cancer screening, information on performance of screening tests is needed, especially in groups with a presumed lower test performance. We compared test performance of immunologic fecal occult blood testing (FIT) and pseudosigmoidoscopy with colonoscopy for detection of advanced adenomas in an average risk screening population. In addition, we explored the influence of gender, age, and location on test performance. FIT was collected prior to colonoscopy with a 50 ng/mL cutoff point. FIT results and complete colonoscopy findings were available from 329 subjects (mean age: 54.6 ± 3.7 years, 58.4% women). Advanced adenomas were detected in 38 (11.6%) of 329 subjects. Sensitivity for advanced adenomas of FIT and sigmoidoscopy were 15.8% (95% CI: 6.0–31.3) and 73.7% (95% CI: 56.9–86.6), respectively. No sensitivity improvement was obtained using the combination of sigmoidoscopy and FIT. Mean fecal hemoglobin in FIT positives was significantly lower for participants with only proximal adenomas versus those with distal ones ($P = 0.008$), for women versus men ($P = 0.023$), and for younger (<55 years) versus older (≥55 years) subjects ($P = 0.029$). Sensitivities of FIT were 0.0% (95% CI: 0.0–30.9) in subjects with only proximal versus 21.4% (95% CI: 8.3–41.0) in those with distal nonadvanced adenomas; 5.3% (95% CI: 0.0–26.0) in women versus 26.3% (95% CI: 9.2–51.2) in men; 9.5% (95% CI: 1.2–30.4) in younger versus 23.5% (95% CI: 6.8–49.9) in older subjects. Sigmoidoscopy had a significantly higher sensitivity for advanced adenomas than FIT. A single FIT showed very low sensitivity, especially in subjects with only proximal nonadvanced adenomas, in women, and in younger subjects. This points to the existence of "low" FIT performance in subgroups and the need for more tailored screening strategies. *Cancer Prev Res; 4(10); 1563–71. ©2011 AACR.*

Introduction

Several nationwide and opportunistic colorectal cancer (CRC) screening initiatives are currently available in Western countries, using different screening modalities such as the guaiac-based fecal occult blood test (FOBT), the immunologic FOBT (FIT), sigmoidoscopy, and colonoscopy (1). Apart from the early diagnosis of asymptomatic CRC, detection of advanced adenomas (i.e., adenomas ≥10 mm in size, containing high-grade dysplasia and/or any villous component) is currently considered an important target of CRC screening (2), as these lesions are associated with an increased risk of malignancy (3). Randomized trials have reported that screening using FOBT and sigmoidoscopy may reduce CRC mortality by 15% to 17% (4, 5) and 31% (6), respectively. Test performance of the semiquantitative FIT appears to be superior to that of the guaiac-based FOBTs (7, 8), but so far, results of randomized controlled trials on the effects of FIT on CRC mortality are lacking. Although many studies assessed the individual performance of FIT or sigmoidoscopy in various populations, only a few were conducted comparing both methods with colonoscopy as a reference standard in screening populations (9, 10). In addition, the impact of age, gender, and location of adenomas on performance of the most commonly used screening tests has not been extensively studied. Studies, applying colonoscopy only for FIT-positive individuals, have reported lower positivity rates and stool hemoglobin (Hb) in women, in younger age groups, and subjects with proximal lesions (7, 11). As in these studies, colonoscopy data were not available from participants with

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a negative FIT, it remains unclear whether this discrepancy reflects a lower adenoma rate or possibly a lower sensitivity of FIT in these subgroups. Primary colonoscopy screening of all FIT positives as well as negatives is needed to obtain this information on sensitivity in subgroups but the number of such studies is limited. Only one screening study comparing FIT positives and negatives with colonoscopy findings did report on gender differences (12), and a second study did report on colonic location in relation to test performance (13). Up to now, an overview of the variables gender, age, and location on screening test sensitivity within the same study population is lacking.

In view of the recent adoption of large-scale, nationwide screening programs using FIT in several Western countries, it is essential to determine potential factors which may affect the performance of these tests and possibly offer the opportunity for developing tailored, more efficient screening strategies in the future.

In this prospective, single-center study, we compared the test performance concerning the detection of advanced adenomas of FIT and sigmoidoscopy with colonoscopy as reference standard in an average risk screening population. In addition, we explored whether demographic features (i.e., age and gender), as well as the anatomic location of adenomas may impact on mean Hb values in stool and on the sensitivity of the FIT.

Methods

Study population

Employees of the Maastricht University Medical Center, aged 50 to 65 years, were invited to participate in a CRC screening trial using primary colonoscopy. Exclusion criteria were severe comorbidity, colonoscopy within the previous 5 years, surveillance after polypectomy or CRC, and development of lower gastrointestinal symptoms in the 3 months prior to colonoscopy. Written informed consent was obtained from all participants. The study protocol was approved by the Dutch Health Council and by the Institutional Medical Ethics Committee (METC-04088).

Immunologic FOBT

A single FIT was offered to all participants in this colonoscopy screening trial. The automated semiquantitative OC-sensor test (Eiken Chemical Co.) was used for the immunologic analysis of Hb in stool. Participants were instructed to scrape different parts of stool from one bowel movement in the 2 weeks prior to colonoscopy and before starting the bowel preparation. Completed FITs were returned to the hospital within 24 hours after collection and stored at −80°C until analysis with the OC-sensor MICRO Desktop Analyzer (Eiken Chemical Co.). Although several CRC screening studies used a 100 ng/mL cutoff value for the OC-sensor FIT (14–16), a cutoff value of 50 ng/mL (corresponding with 10 μg/g) has also been reported (7, 17, 18), resulting in a higher sensitivity for detection of advanced adenomas (16). Therefore, we decided to use a cutoff value of 50 ng/mL to determine positivity.

Colonoscopic procedure and sigmoidoscopy findings

Bowel cleansing consisted of 4 L hypertonic polyethylene glycol solution (Klean-Prep, Norgine Europe B.V.). Four experienced endoscopists carried out all the procedures and recorded endoscopic findings, including quality indicators (19) in a standardized registration form. Conscious sedation was administered using midazolam and pethidine intravenously. A 4-point scale was used to rate bowel preparation (i.e., "excellent," "good," "fair," or "poor-inadequate"). After cecal intubation, a 20-mg bolus of butyl bromide was administered intravenously for optimal visualization of the colon during retraction. Polyp size and location were registered. The proximal colon was defined as cecum, ascending colon, hepatic flexure, transverse colon, and splenic flexure, and the distal colon was defined as descending colon, sigmoid, and rectum. Finally, colorectal polyps were removed by cold biopsy, snare polypectomy, or endoscopic mucosal resection.

One experienced gastrointestinal pathologist revised all lesions. Adenomas with a size 10 mm or greater, any villous component, and/or high-grade dysplasia were classified as advanced adenomas (3).

In case of incomplete colonoscopy, participants were offered additional CT-colonography to visualize the entire colon.

For the purpose of this study, we separately registered sigmoidoscopy findings (i.e., pseudosigmoidoscopy), which were deducted from the colonoscopy reports and defined as an endoscopic examination of the distal colon (rectum, sigmoid, and descending colon). Sigmoidoscopy screening was regarded as a positive examination, in case of 1 or more adenoma(s) in the distal colon. According to current guidelines, subjects with at least 1 adenoma detected by sigmoidoscopy screening should undergo a colonoscopy. Subjects with lesions in the proximal colon, having at least 1 advanced and/or nonadvanced adenoma in the distal colon were therefore defined as detected by sigmoidoscopy.

Data analysis

Sample size calculation was conducted on the basis of previously reported prevalence rates for advanced adenomas in average risk groups (20), as well as sensitivities of FIT (10, 13) and sigmoidoscopy (10, 21, 22) for detection of subjects with advanced adenomas. With an α of 0.05 and 80% power, a sample of at least 300 subjects was needed to detect a minimal expected difference of 30% in sensitivity for detection of advanced adenomas between FIT and sigmoidoscopy. For the purpose of this study, only subjects with available FIT results and a complete colonoscopy were included in the final analysis. As we could not anticipate these factors before starting the study, inclusion continued for the duration that financial resources were available, resulting in a total enrollment of 447 participants. Sensitivity, specificity, positive and negative predictive values

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(PPV and NPV) with 95% CIs were calculated for FIT and sigmoidoscopy, using colonoscopy as reference. For FIT, test performance was calculated for the total population with subgroup analyses to address the potential impact of gender, age, and colonic adenoma location on the outcome of FIT. As the starting age for CRC screening varies between 50 and 55 years in different countries, the age groups younger than 55 years and 55 years or older were analyzed separately. As subjects with proximal advanced and/or nonadvanced adenomas only would have been missed by sigmoidoscopy and are hypothetically more difficult to detect by FIT, the study subjects were subdivided according to location of adenomas into subjects with adenomas in the proximal colon only and those with at least 1 distal lesion with or without a proximal lesion. Dichotomous variables were compared using a χ^2 test with Fisher's exact test when necessary. The normality of distribution of continuous variables was tested using the Kolmogorov–Smirnov test. Comparisons between parametric continuous variables were made using a Student's *t* test and between nonparametric variables using a Mann–Whitney *U* test. Receiver operating characteristic (ROC) curves were used to determine sensitivity and specificity of FIT at various cutoff levels. All tests were conducted using SPSS version 15.0 (SPSS Inc) and a *P* value below 0.05 was considered statistically significant using 2-sided tests.

Results

Population and colonoscopy data

In total, 1,090 subjects were invited, and with a participation rate of 41.0%, 447 primary screening colonoscopies (mean age participants: 54.6 ± 3.6 years, 60.6% women) were carried out. Bowel preparation was rated as excellent in 51.9%, good in 34.2%, fair in 11.8%, and poor-inadequate in 2.0%. The crude cecal intubation rate was 90.5% in the total population, and the mean withdrawal time was 12 ± 2 minutes for all colonoscopies and 11 ± 2 minutes in those without lesions. The adenoma detection rate was 25.6% for the total population. Men had, in comparison with women, significantly more often adenomas (33.5% vs. 20.3%; $P = 0.003$) as well as advanced adenomas (15.3% vs. 8.9%; $P = 0.047$). Thirty-seven participants with an incomplete colonoscopy all consented to CT-colonography, which revealed no additional colonic lesions.

For 329 of the 447 participants (73.6%) who underwent a screening colonoscopy, complete colonoscopy and FIT data were available. The colonoscopy data from these 329 participants (mean age: 54.6 ± 3.7 years, 58.4% women) will be used for the comparison of FIT and pseudosigmoidoscopy. The results about the diagnostic yield of the 3 screening methods will be displayed for a per subject analysis followed by a per adenoma analysis. FIT results were not available from the 1 participant with CRC and therefore this CRC case was not included in the analysis.

Colonoscopy: general diagnostic yield

In the group of 329 participants, colonoscopy detected a total of 86 participants with adenomatous lesions (26.1%), 48 with nonadvanced adenomas (14.6%) and 38 with advanced adenomas (11.6%; Table 1).

In these 86 participants with adenomas, 167 adenomas were detected (107 nonadvanced and 60 advanced adenomas). Of the 60 advanced adenomas, 23 (38.3%) were less than 6 mm in size, 7 (11.7%) between 6 and 10 mm, and 30 lesions (50.0%) were 10 mm or greater.

Colonoscopy findings: relation to location

Within the group of 86 participants with adenomas, 27 (31.4%) had only proximally located adenoma(s) and 59 (68.6%) had at least 1 distal adenoma.

A total of 34 adenomas were detected in the group with proximal advanced and/or nonadvanced adenomas only (27 subjects), and a total of 133 adenomas in the group with at least 1 distal advanced and/or nonadvanced adenoma (59 subjects). This resulted in a significantly lower mean number of adenomas per participant in the "proximal only" in comparison with the "distal" group (1.3 ± 0.6 vs. 2.1 ± 1.5; $P = 0.002$). The mean adenoma size was smaller in the group with only proximal adenomas compared with those with at least 1 distal adenoma

Table 1. Prevalence of subjects with adenomas categorized by the most advanced adenoma detected per participant, in the group with complete colonoscopy and FIT result available ($n = 329$)

	Total $n = 329$ (%)	Men $n = 137$ (%)	Women $n = 192$ (%)	*P*
Adenomatous lesions	86 (26.1)	43 (31.4)	43 (22.4)	0.075
Nonadvanced				
Nonvillous, low grade, <1 cm	48 (14.6)	24 (17.5)	24 (12.5)	0.209
Advanced	38 (11.6)	19 (13.9)	19 (9.9)	0.296
Nonvillous, low grade, >1 cm	2	0	2	
Nonvillous, high grade	7	6	1	
Tubulovillous, low grade	25	10	15	
Tubulovillous, high grade	4	3	1	

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(5.7 ± 6.7 vs. 6.8 ± 5.8 mm; $P = 0.043$). When taking only proximal adenomas into account, the mean size of proximal adenomas did not differ between the "proximal only" group and the group with at least 1 distal adenoma (5.7 ± 6.2 vs. 6.2 ± 5.2 mm; $P = 0.132$).

Colonoscopy findings: relation to gender and age

Of 329 participants, 43 (31.4%) of 137 men and 43 (22.4%) of 192 women had adenomas. Advanced adenomas were present in 19 men (13.9%) and 19 women (9.9%; Table 1).

The percentage of men and women with only proximal advanced and/or nonadvanced adenomas was comparable (27.9% vs. 32.6%; $P = 0.815$). The age groups younger than 55 years and 55 years or older did not differ in advanced or total adenoma prevalence, nor location of advanced or total adenomas.

The location, number, and size of advanced or total adenomas did not significantly differ between men and women, nor between age groups younger than 55 and 55 years or older (data not shown).

FIT: general diagnostic yield

In the 329 participants, the FIT positivity rate at a cutoff point of 50 ng/mL was 4.6% ($n = 15$) with a mean fecal Hb concentration in FIT-positive subjects of 470.7 ± 657.3 ng/mL (Table 2). In our population ($n = 329$), FIT (including hypothetical follow-up colonoscopy after a positive FIT) would have detected only 6 of the 38 participants with advanced adenomas (1.8% detection rate), resulting in a sensitivity of 15.8% (Table 3). Specificity, PPV, and NPV are given in Table 4.

In the per adenoma analysis, FIT (cutoff value: 50 ng/mL) would have missed 71.3% of all advanced adenomas (Table 5).

Sigmoidoscopy: general diagnostic yield

Sigmoidoscopy (including hypothetical follow-up colonoscopy after a positive sigmoidoscopy result) would have detected 28 of the 38 participants with advanced adenomas (detection rate: 8.5%), resulting in a sensitivity of 73.7%. (Tables 3 and 4). One third ($n = 5$) of all subjects with proximal advanced adenomas ($n = 15$) had simultaneous distal adenomas and were therefore within the reach of sigmoidoscopy screening, considering the guidelines that subjects with a positive sigmoidoscopy subsequently have to undergo a total colonoscopy. Of the total of 60 advanced adenomas detected by colonoscopy screening, sigmoidoscopy would have missed 12 (20.0%) lesions (Table 5).

Comparison of sigmoidoscopy with FIT

The sigmoidoscopy would have resulted in a significantly higher sensitivity than FIT (Table 4; $P = 0.000$). All individuals with advanced adenomas detected by FIT ($n = 6$) were also detected by sigmoidoscopy, indicating that combining sigmoidoscopy with FIT is not of any additional diagnostic value (Tables 3–Table 5). In the per adenoma analysis, the proportions of (advanced) adenomas ($n = 60$) missed or detected by FIT and sigmoidoscopy are displayed in Table 5.

The influence of colonic location, gender, and age on FIT test performance

Location. The participants with proximal advanced and/or nonadvanced adenomas only had significantly lower FIT positivity rate (0% vs.11.7%; $P = 0.016$) and mean fecal Hb content (3.0 ± 9.1 vs. 99.1 ± 375.2 ng/mL; $P = 0.008$) than those having at least 1 distal adenoma (Table 2). Importantly, in our study, FIT missed all the participants with advanced adenomas in the "proximal only" group ($n = 10$) and 22 of 28 advanced adenoma subjects in the "distal" group, resulting in sensitivities of 0.0% and 21.4%, respectively (Table 6). ROC analyses were used to determine the cutoff value for the "proximal only" group with which FIT could reach a sensitivity comparable with the sensitivity obtained in the "distal group" at 50 ng/mL (21.4%). A cutoff value of 27.5 ng/mL resulted in a sensitivity of 20.0% for the FIT in the "proximal only" group. Sensitivity, specificity, PPV, and NPV for the different cutoff values are given in Table 6.

Gender. The positivity rate of FIT was 2.6% in women and 7.3% in men ($P = 0.060$) at a cutoff point of 50 ng/mL and was significantly lower in women than in men at a cutoff of 100 ng/mL (1.0% vs. 5.8%, Table 2; $P = 0.019$). Not only was the FIT positivity rate lower in women but also in the participants with a positive FIT, the mean fecal Hb concentration was also lower in women than in men (95.5 ± 24.1 vs. 770.9 ± 768.3 ng/mL, Table 2; $P = 0.023$). In line with this observation, FIT missed 18 of 19 women and 14 of 19 men with advanced adenomas, with resulting sensitivities of 5.3% and 26.3%, respectively (Table 6).

On the basis of gender-specific ROC curves, in women, a cutoff value of 27.5 ng/mL would have been required to reach a sensitivity comparable with that in men at 50 ng/mL (i.e., 26.3%; Table 6).

Age. There were no significant differences in FIT positivity rate between age groups (Table 2). However, within the group with a positive FIT, the mean fecal Hb content was significantly lower in subjects younger than 55 years versus those 55 years or older (239.7 ± 393.7 vs. 805.8 ± 825.1 ng/mL, Table 2; $P = 0.029$). FIT missed 19 of 21 participants less than 55 years and 13 of 17 participants 55 years or older with advanced adenomas, resulting in sensitivities of 9.5% and 23.5%, respectively. On the basis of ROC curves, again, a cutoff value of 27.5 ng/mL was needed to reach a similar sensitivity in the younger (i.e., 23.8%) than the older group at a cutoff value of 50 ng/mL (Table 6).

Discussion

In this average risk screening population, FIT had a very low sensitivity for the detection of subjects with advanced adenomas, especially in women and younger subjects; FIT also missed all subjects with such lesions confined to the proximal colon only. Furthermore, sigmoidoscopy as

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Table 2. Positivity rates and mean Hb values of FIT in relation to location of adenomas, gender, and age in the group of 329 participants with a complete screening colonoscopy and available FIT results

		Location			Gender			Age		
	Total	Proximal only[a]	≥1 Distal[a]	*P*[b]	Women	Men	*P*[b]	<55 y	≥55 y	*P*[b]
Positivity rate, %										
100.0 ng/mL	3	0	8.3	0.064	1	5.8	***0.019***	1.8	4.5	0.203
50.0 ng/mL	4.6	0	11.7	***0.016***	2.6	7.3	0.06	4.1	5.1	0.793
27.5 ng/mL	7.9	7.7	18.3	***0.012***	5.7	10.9	0.099	7	8.3	0.682
Concentration Hb, ng/mL										
In group with positive FIT	470.7 ± 657.3	***None***	808.9 ± 847.0	n/a	95.5 ± 24.1	770.9 ± 768.3	***0.023***	239.7 ± 393.7	805.8 ± 825.1	***0.03***
In group with adenomas	70.0 ± 315.7	3.0 ± 9.1	99.1 ± 375.2	***0.008***	18.6 ± 2.8	133.1 ± 439.6	0.127	33.8 ± 173.6	104.6 ± 407.2	0.303
In group with adenomas ≥10 mm	319.7 ± 643.8	9.3 ± 16.2	381.7 ± 691.7	0.106	26.1 ± 32.7	686.6 ± 853.3	0.088	146.2 ± 368.9	493.1 ± 822.7	0.503
In group with advanced adenomas	153.1 ± 464.8	7.1 ± 13.9	205.3 ± 534.2	0.082	14.7 ± 26.3	291.6 ± 634.8	0.635	63.4 ± 244.6	263.9 ± 633.5	0.303

[a]Proximal group consists of subjects with proximal adenomas only, distal group of subjects with at least 1 distal adenoma, for the calculation of positivity rates subjects without colonic pathology were added to the proximal and the distal group, resulting in a total number of subjects of 269 and 303, respectively.
[b]On the basis of χ^2 forth comparison of positivity rates and on the Mann–Whitney *U* test for mean Hb stool concentration.

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Table 3. Percentage of subjects with adenomas and subjects with advanced adenomas detected by colonoscopy screening, missed and/or detected by sigmoidoscopy and FIT

Subjects with adenomas ($n = 86$)		
	Sigmoidoscopy	
	Positive	Negative
FIT positive	7 (8.1%)	0
FIT negative	52 (60.5%)	27 (31.4%)
Subjects with advanced adenomas ($n = 38$)		
	Sigmoidoscopy	
	Positive	Negative
FIT positive	6 (15.8%)	0
FIT negative	22 (57.9%)	10 (26.3%)

Table 5. Percentage of all adenomas and all advanced adenomas detected by colonoscopy screening, missed and/or detected by sigmoidoscopy and FIT

All adenomas ($n = 167$)		
	Sigmoidoscopy	
	Positive	Negative
FIT positive	29 (17.3%)	0
FIT negative	104 (62.3%)	34 (20.4%)
All advanced adenomas ($n = 60$)		
	Sigmoidoscopy	
	Positive	Negative
FIT positive	17 (28.3%)	0
FIT negative	31 (51.7%)	12 (20.0%)

Table 4. Test performance of FIT and sigmoidoscopy[a] for the detection of subjects with adenomas ($n = 86$) and those with advanced adenomas ($n = 38$)[b] in an average risk screening population ($n = 329$)

	Adenomas % (95% CI)	Advanced adenomas % (95% CI)
Sigmoidoscopy		
Sensitivity	68.6 (57.7–78.2)	73.7 (56.9–86.6)
Specificity	100 (98.5–100.0)	89.3 (85.2–92.7)
PPV	100 (93.2–100.0)	47.5 (34.3–60.9)
NPV	90 (85.8–93.3)	96.3 (93.3–98.2)
FIT, 50 ng cutoff		
Sensitivity	8.1 (3.3–16.1)	15.8 (6.0–31.3)
Specificity	96.7 (93.6–98.6)	96.9 (94.2–98.6)
PPV	46.7 (21.3–73.4)	40 (16.3–67.7)
NPV	74.8 (69.7–79.6)	89.8 (85.9–92.9)
FIT, 27.5 ng cutoff		
Sensitivity	15.1 (8.3–24.5)	29 (15.4–45.9)
Specificity	94.7 91.0–97.1)	94.9 (91.6–97.1)
PPV	50 (29.9–70.1)	42.3 (23.4–63.1)
NPV	75.9 (70.7–80.6)	91.1 (87.3–94.1)

[a]Defined as positive in case of colonoscopic findings located in the distal colon (i.e., rectum, sigmoid, and colon descendents) which would have led to a follow-up colonoscopy.

[b]Defined as lesions having size 10 mm or more, a villous component, and/or high-grade dysplasia.

primary screening instrument would have resulted in a very high sensitivity for the detection of advanced adenomas. In view of the recent implementation of several nationwide screening programs using FIT in Western countries, it is important to address potential factors which may affect performance of these tests, as this knowledge may help to design tailored screening strategies. In our study conducted in subjects with average risk, the adenoma detection rate, one of the quality indicators for colonoscopy, was 26% and is in line with previously published data ranging from 21% to 29% (23–25). It should be acknowledged that colonoscopy has a miss rate of up to 22% for polyps of any size, as has been reported by a recent meta-analysis of back-to-back colonoscopy studies (26). The sensitivity of the OC-sensor FIT for the detection of subjects with advanced adenomas we found was 16%, which is remarkably lower than sensitivities observed in 2 other studies using the same test for a single screening (36% and 38%; refs. 14, 27). One should take into account, however, that these studies have been conducted in populations quite different from our study population, as both studies investigated symptomatic subjects with a higher mean age than our group (14, 27). It is known that FITs carried out in symptomatic subjects yield higher sensitivities (28). Several studies have reported on test performance of FIT in asymptomatic and average risk screening subjects undergoing colonoscopy screening (8–10, 12, 13, 29–31). These studies have used different types of FIT. This hampers a direct comparison of test results because the different types of FIT are known to vary considerably in sensitivity, from 25% to 72%, within the same population (8). Overall, the sensitivity of the OC sensor we used for the detection of subjects with advanced adenomas was in the lower range than in studies using

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Table 6. Test performance of FIT to detect subjects with advanced adenomas (i.e. villous component, high-grade dysplasia, and/or size ≥10 mm), subdivided for location, gender, and age groups

	Detection of subjects with advanced adenomas					
	Location		Gender		Age group	
	Proximal only[a] % (95% CI)	≥1 Distal[a] % (95% CI)	Women % (95% CI)	Men % (95% CI)	<55 y % (95% CI)	≥55 y % (95% CI)
FIT (50.0 ng/mL)						
Sensitivity	0.0 (0.0–30.9)	21.4 (8.3–41.0)	5.3 (0.0–26.0)	26.3 (9.2–51.2)	9.5 (1.2–30.4)	23.5 (6.8–49.9)
Specificity	96.9 (94.0–98.7)	96.7 (93.9–98.5)	97.7 (94.2–99.4)	95.8 (90.2–98.6)	96.7 (92.5–98.9)	97.1 (92.8–99.2)
PPV	0.0 (0.0–36.9)	40.0 (16.3–67.7)	20.0 (0.5–71.6)	50.0 (18.7–81.3)	28.6 (3.7–71.0)	50.0 (15.7–84.3)
NPV	96.2 (93.1–98.2)	92.4 (88.8–95.2)	90.4 (85.2–94.2)	89.0 (82.2–93.8)	88.6 (82.7–93.0)	91.2 (85.5–95.2)
FIT (27.5 ng/mL)						
Sensitivity	20.0 (2.5–55.6)	32.1 (15.9–52.4)	26.3 (9.2–51.2)	31.6 (12.6–56.6)	23.8 (8.2–47.2)	35.3 (14.2–61.7)
Specificity	95.0 (91.6–97.3)	94.6 (91.2–96.9)	96.5 (92.6–98.7)	92.4 (86.0–96.5)	94.7 (89.9–97.9)	95.0 (89.9–98.0)
PPV	13.3 (1.7–40.5)	37.5 (18.8–59.4)	45.5 (16.8–76.6)	40.0 (16.3–67.7)	38.5 (13.9–68.4)	46.2 (19.2–74.9)
NPV	96.9 (93.9–98.6)	93.2 (89.6–95.9)	92.3 (87.4–95.7)	89.3 (82.5–94.2)	90.0 (84.3–94.2)	92.3 (86.7–96.1)

[a]Location groups defined as subjects with proximal adenomas only, and those with at least 1 distal adenoma (irrespective of proximal lesions), for the calculation of specificity, PPV, NPV, and subjects without adenomas were added to both groups, resulting in a total number of subjects of 269 and 303, respectively.

other FITs (8, 10, 30). This difference in test outcome may be related to several other factors apart from the different types of FIT. First, several studies reporting on FIT sensitivity have conducted testing not on a single day but on multiple days, which certainly results in higher test sensitivity (29). Second, our population was characterized by a higher percentage of female participants, and it is known that in women, FIT shows lower sensitivity rates (12). Third, in most other studies, populations were of older age. We hypothesize that because of the lower mean age of our population, a lower prevalence of large lesions was found, in effect, 38% of advanced adenomas had size less than 6 mm whereas larger adenomas are more easy to detect by FIT (10). In our study, the sensitivity of FIT for subjects with large adenomas (≥10 mm) was 33%, which is in line with data from other studies (20% and 33%; refs. 10, 13). In the present study, sigmoidoscopy would have reached a sensitivity of 74% for the detection of advanced adenomas, which is comparable with data from other studies conducted in average risk populations (54%–83%; refs. 9, 10, 22, 32). The definition of what is considered as upper border of the colon reached during sigmoidoscopy differs among studies (33). We considered the splenic flexure as a clear landmark, thereby reporting endoscopic findings from rectum up to splenic flexure as being detected by sigmoidoscopy. When considering the sigmoidoscopy as confined to the rectosigmoid region, one should realize that the transition from sigmoid to descending colon is less obvious as landmark. Using the latter definition, sensitivity for the detection of advanced adenomas would have been 66% compared with the 74% sensitivity of sigmoidoscopy up to the splenic flexure. Of the subjects with proximal advanced adenomas, one third also had simultaneous distal adenomas, and therefore these proximal advanced adenomas would have been detected during subsequent colonoscopy. A similar approach (i.e., considering proximal advanced lesions as being in reach of sigmoidoscopy screening when distal adenoma(s) were present) has also been applied by others (9, 33). Consequently, two third of the subjects with proximal adenomas would not have been detected, which is in line with previous reports (9, 33).

Sigmoidoscopy had a significantly higher sensitivity for the detection of advanced adenomas than FIT (i.e., 58% difference). Four other studies have compared FOBT and/or FIT and sigmoidoscopy with colonoscopy findings (9, 10, 21, 22), of which 2 used a single FIT. Graser and colleagues reported a similar difference of 51% FIT and sigmoidoscopy for the detection of advanced adenomas (10) whereas Cheng and colleagues (9) and the 2 remaining studies using guaiac-based FOBT did not report on sensitivities for advanced adenomas separately (21, 22). Furthermore, one of the FOBT studies included 97% men, which hinders a direct comparison (21). Our data show that stool testing only marginally increases sensitivity when combined with sigmoidoscopy, in line with previous findings (10, 21, 22). FIT lacked sensitivity in subjects with proximal advanced and/or adenomas only, an observation in line with those of Morikawa and colleagues (13). This negative result may be influenced by several factors contributing to a lower Hb concentration in stool. First, because of an increased degradation of Hb in case of a proximal lesion during colonic passage (11) and second because of the lower mean number and size of adenomas

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in the "proximal" group. Proximal CRCs have molecular characteristics different from distal CRCs, and proximal CRCs have an increased mortality risk (independent of factors such as stage, tumor size, grade, lymph node disease, and number of lymph nodes; refs. 34, 35). One should realize that all advanced adenomas in subjects with proximal lesions only were missed by sigmoidoscopy but also by FIT. The effectiveness of colonoscopy screening in the reduction of CRC-related mortality for proximal CRC is currently under debate (36), as several follow-up studies after colonoscopy have shown a reduction of mortality caused by distal CRCs but not for proximal CRCs (37, 38). In the present population, single FIT had a lower sensitivity for the detection of subjects with advanced adenomas in women versus men. This is in line with findings of Brenner and colleagues (12), although these authors reported on test performance for the detection of advanced neoplasms and not for advanced adenomas. The lower sensitivity of FIT in women is an intriguing and relevant finding, which should be further evaluated. In addition, women had substantially and significantly lower mean Hb concentrations in stool. This lower Hb content in stool of female participants has also been reported by 2 other groups. The first study included only FIT-positive individuals and did not allow for the calculation of FIT sensitivity (11). The second study was a colonoscopy screening study by Brenner and colleagues (12). The difference in stool Hb content between male and female participants might partly be explained by a higher frequency of (advanced) adenomas in men. On the basis of our data, we can conclude that the lower detection rate of advanced adenomas by FIT in women is not only caused by a lower adenoma prevalence in women, as suggested by others (7, 39) but in addition is influenced by gender differences in test performance, with lower stool Hb concentrations in female participants having (advanced) adenomas.

Considering the lower sensitivity of FIT in the group with only proximal advanced and/or nonadvanced adenomas, women, and subjects younger than 55 years, a change in the cutoff level to 27.5 ng/mL resulted in an improvement in sensitivity toward the level reached in the other groups at a 50 ng/mL cutoff point.

A limitation of the present study is the population size ($n = 329$). Our primary aim was to compare the sensitivity of single FIT and of sigmoidoscopy with colonoscopy. The study was powered to detect a minimal expected difference of 30% between sigmoidoscopy and FIT. Furthermore, our population size is in the range of that in 2 similar type screening studies ($n = 307$ and $n = 505$; refs. 10, 21).

Our data showing lower FIT sensitivity and fecal Hb concentration in women, subjects under 55 years of age, and subjects with proximal located adenomas only should be confirmed in larger average risk screening populations with adequate numbers of participants in the subgroups, using colonoscopy as a reference standard. With the increasing number of countries using FIT as a population-based CRC screening method (1), knowledge on sensitivities of FIT in subgroups is very relevant and may result in adjusted or alternative screening strategies in these subgroups. This may include using alternative screening methods or lowering the FIT cutoff value in certain subgroups and/or increasing the screening initiation age toward 55 years.

A limitation of the present study design is that single FIT screening was evaluated, although the efficacy of a FIT-based screening program requires annual or biennial, that is, repeated FIT. Studies using 1 or 2 additional test days for FIT have shown an increase in sensitivity, probably due to intermittent bleeding of adenomas (29). The question arises whether the small advanced adenomas in the present study would have been bleeding at all. In conclusion, a single FIT with a cutoff value of 50 ng/mL showed a very low sensitivity, missing 84% of subjects with advanced adenomas detected by colonoscopy. FIT especially lacked sensitivity in subjects with only proximal advanced adenomas, in women, and in subjects under the age of 55 years. Sigmoidoscopy when used as screening instrument would have resulted in a very high sensitivity for the detection of advanced adenomas, superior to FIT. Our findings point to the existence of "low" FIT performance in specific subgroups and emphasize the need for more tailored screening strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Test Performance of Immunologic Fecal Occult Blood Testing and Sigmoidoscopy Compared with Primary Colonoscopy Screening for Colorectal Advanced Adenomas

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