Lower Risk of Advanced Neoplasia Among Patients With a Previous Negative Result From a Fecal Test for Colorectal Cancer

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See Alquist DA et al on page 272 in CGH; see editorial on page 422.

**BACKGROUND & AIMS:** Consecutive rounds of fecal occult blood tests (FOBTs) are used to screen for colorectal cancer (CRC); they detect precursor lesions and early-stage disease. We assessed whether the positivity rate and the positive predictive values (PPVs) for advanced neoplasia and CRC decrease with repeated testing by using fecal immunochemical tests (FITs). **METHODS:** Data were collected from 2 rounds of screening. In the first round, average-risk persons (50 to 74 years old) were randomly assigned to groups that received the guaiac FOBT or FIT. In the second round, the subjects received only FIT (1594 received FIT after guaiac FOBT and 2022 received FIT after FIT). The positivity rate and PPV for advanced neoplasia and CRC were compared between second-round participants with a previous negative test result (FIT after guaiac FOBT or FIT after FIT) and first-round participants (guaiac FOBT or FIT). **RESULTS:** The rate of positive results from FIT was 7.4% in the FIT-after-FIT group, compared with 8.1% in the first-round FIT group (P = .34). A significant decrease was observed in the PPV for advanced neoplasia between the first and second round from 55% (132/239) to 44% (112/252; P = .017). The PPV for CRC was 8% (20/239) in the first round versus 4% (9/252) in the second round (P = .024). Ten interval cancers were diagnosed. There were no significant differences in stages of cancers detected in the first and second round or the interval cancers. **CONCLUSIONS:** The rate of positive results from FIT does not decrease after repeated CRC screening, but the PPVs of FIT for advanced neoplasia and for CRC are significantly lower among second-round participants who tested negative in the first round.

**Keywords:** Diagnostic Yield; Average-Risk Population; Colon Cancer Screening; Efficacy.

**Abbreviations used in this paper:** CRC, colorectal cancer; FIT, fecal immunochemical test; FOBT, fecal occult blood test; PPV, positive predictive value.

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Mass screening programs for colorectal cancer (CRC) are aimed at decreasing the mortality and morbidity of CRC. Several methods of screening for CRC are available, including fecal occult blood tests (FOBTs), flexible sigmoidoscopy, and colonoscopy. To date, only 2-step screening programs such as FOBT-based screening and sigmoidoscopy screening have a documented effectiveness in reducing disease-specific mortality.1–4

The efficiency of any 2-step screening program depends on the ability of the initial screening test to detect target lesions. A good initial screening test should have a small number of false-positive test results and, even more importantly, a small number of false-negative test results in patients with CRC. Both the guaiac FOBT and the fecal immunochemical test (FIT) have a high sensitivity for CRC but are less well able to detect advanced adenomas.5–9

Most data on the performance of FOBT-based screening programs stem from randomized controlled trials that used the guaiac test only.2–4 Two studies in an asymptomatic population in which all participants underwent colonoscopy reported a sensitivity of the guaiac test for cancer of 13% and 25%. This is in line with the results of a study of Graser et al, who found a sensitivity of 20% for the guaiac test.10 Specificities for cancer were 95% and 80%.11,12

It has recently been shown that the FIT, which uses enzyme immunoassays detecting human hemoglobin, has better test characteristics and is associated with a higher participation rate.13–16 The gain in sensitivity compared with the guaiac FOBT seems higher for advanced adenomas than for cancers.17,18 The FIT has other advantages over the older guaiac FOBT, such as the absence of dietary restrictions and the quantitative nature of the test, with the ability to vary the positivity threshold. Little is known, however, about the performance of FIT in consecutive screening rounds.

The aim of the study reported here was to evaluate the performance of FIT in a second round of CRC screening. We recently completed 2 rounds of a Dutch FOBT-based screening pilot in asymptomatic persons aged 50 to 74 years. During the first round, invitees were randomized to receive either a guaiac FOBT or a FIT.15 In the second round, only the FIT was used. We hypothesized that the positivity rate would be lower in the second round and...
that fewer cases of CRC and advanced neoplasia would be detected in second-round FIT-positive participants who had tested negative in the first round compared with first-round test-positive participants. We expected a more pronounced decrease for cancers than for advanced adenomas.

Subjects and Methods

Two consecutive screening rounds have been completed in a fecal test–based CRC pilot screening program in the Amsterdam region of The Netherlands. The first round was conducted in 2006. In this first round, 10,054 invitees were randomized to receive either a guaiac FOBT or a FIT. The second round used FIT only and was performed among 10,258 persons in 2008 (trial registration no. NTR1327). Ethical approval was provided by the Dutch Health Council (2005/03WBO, The Hague, The Netherlands). The study designs of the first and second rounds have been reported in detail elsewhere. A summary is given in the following text.

Population and Design

Asymptomatic persons aged 50 to 74 years and living in the catchment area of the pilot program were eligible for invitation to the screening program. Symptomatic persons were advised not to participate in the program but to contact their general physician. The catchment area comprised 3 postal code areas within the surroundings of Amsterdam.

A file containing all eligible persons based on birth date and postal code was extracted by the municipalities from the population database. A random sample of this file was invited through an invitation letter by postal mail. Invitations were coordinated by the regional Comprehensive Cancer Center Amsterdam, an organization that is also responsible for the logistics of the nationwide breast and cervical cancer screening programs in The Netherlands.

Persons with a positive test result in the first round were excluded from participation in the second round. In case of adenomas, these test-positive persons were enrolled in a surveillance program according to the Dutch guidelines. In case of CRC, they were referred to the departments of oncology and/or surgery of our hospital for treatment. Other individuals who no longer fulfilled eligibility criteria at the start of the second round did not receive an invitation for the second round. This concern persons older than 74 years or persons who had moved out of the catchment area.

Invitation Procedure

An invitation kit with the stool test was sent by postal mail. The invitation letter was signed by the principal investigator. In addition to the invitation letter, the kit also contained a detailed information brochure, a test instruction leaflet, and a postage-free return envelope. Participants could perform the test at home and return it by postal mail. A signed informed consent form had to be enclosed in the return envelope. A reminder letter was sent to nonresponders at 6 weeks and at 3 months.

Stool Tests

Guaiac FOBT. The guaiac FOBT used in the first round was the Hemoccult II (Beckman Coulter Inc, Fullerton, CA). No dietary instructions were given. Persons were instructed to collect 2 samples of 3 consecutive bowel movements. Cards were developed and read by 2 trained laboratory technicians. Cards were not rehydrated. A test result was considered positive if one or more of the 6 samples showed a blue discoloration.

FIT. The FIT that was used in both rounds was the OC-Sensor by Eiken (Tokyo, Japan). After arrival at the laboratory, tests were stored at 4°C and processed in batches by using an automated clinical analyzer (OC-Sensor Micro; Eiken). A single test was used on one occasion, and a hemoglobin value of 50 ngHb/mL was used as the threshold for test positivity.

Colonoscopy

All participants with a positive test result received a mailed invitation for a consultation at the screening center. During this consultation, the positive test result was explained and, in the absence of contraindications, a colonoscopy was advised. Contraindications for colonoscopy were imaging of the colon within the past 2 years (colonoscopy or computed tomographic colonography), a life expectancy of less than 5 years, or severe comorbidity. The cost of colonoscopy was covered by the participants’ health insurance company.

Colonoscopies were scheduled within 2 weeks after the consultation and were performed by experienced endoscopists. All persons were routinely offered conscious sedation using intravenous midazolam 0.5 mg and/or fentanyl 0.01 mg. Polyethylene glycol solution (2 L; MoviPrep(r), Salix Pharmaceuticals, Morrisville, NC) combined with bisacodyl 10 mg orally was used for bowel preparation. During the procedures, a research assistant was present to record key performance indicators. Size, location, and type of treatment were recorded for all lesions. Lesion size was estimated by using a 7-mm open biopsy forceps. Location was considered distal if the lesion was located distal from the splenic flexure. Indigo carmine staining and/or scopolamine 20 mg were used on endoscopists’ request only. All lesions were preferably removed endoscopically during the first procedure and reviewed histopathologically.

Pathology

All biopsy specimens, polyps, and excision specimens were examined by one experienced pathologist. Histology, grade of dysplasia, and involvement of margins were reported for all lesions. An advanced adenoma was defined as any adenoma ≥10 mm or an adenoma with a villous component >20% or with high-grade dysplasia. Cancer was defined as CRC with invasion beyond the muscularis mucosa. Cancers were staged according to the 5th edition of the American Joint Committee on Cancer classification. Formerly used categories such as carcinoma in situ and intramucosal carcinoma were classified as high-grade dysplasia. Sessile serrated and traditional serrated lesions were classified as adenomas. Nonneoplastic lesions included hyperplastic polyps and inflammatory polyps.

Data Analysis

In this analysis, we evaluated the accuracy of FIT in second-round participants who had also participated in the first round. This means that only data from second-round participants with a negative test result in the first round were included. The accuracy results in this group were compared with the accuracy estimates for the FIT and for the guaiac FOBT obtained in all first-round screening participants. Primary outcome measures were the positivity rate, the positive predictive value (PPV) for CRC, and the PPV for advanced adenomas and CRC combined (hereafter referred to as advanced neoplasia).

The positivity rate was calculated as the number of positive test results relative to the number of tests returned. The PPV was
calculated as the number of persons with the finding of interest relative to the number of persons with a positive test result and a complete colonoscopy. In case of multiple lesions in the same patient, colonoscopy results were classified according to the most advanced lesion per patient.

The group of first-round participants was subdivided into those allocated to guaiac FOBT (the first-round guaiac FOBT group) and those allocated to FIT (the first-round FIT group). The group of second-round participants was subdivided into those with a previous negative guaiac FOBT result (the FIT-after-guaiac FOBT group) and those with a previous negative FIT result (FIT-after-FIT group).

Group differences in positivity rate and in PPV were tested for statistical significance using the \( \chi^2 \) test statistic and expressed as relative risks with corresponding 95% confidence intervals. We hypothesized that the positivity rate and the PPV for CRC and for advanced neoplasia would be lower in second-round participants compared with first-round participants. Because the FIT has a higher sensitivity for CRC than for advanced adenomas, we expected this decrease to be most pronounced for CRC. Differences between male and female subjects in positivity rate and PPV were evaluated using the \( \chi^2 \) test statistic in FIT users of both rounds.

A secondary outcome measure was the interval cancer rate, which was defined as the proportion of cancers diagnosed in first-round participants (both guaiac FOBT and FIT) outside the screening protocol but within the screening interval. Interval cancers were identified through cross-linkage of the screening pilot database with the Dutch cancer registry. Of all identified cancer cases, location (proximal or distal), date of diagnosis, and cancer stage at diagnosis according to the 5th edition of the American Joint Committee on Cancer classification were retrieved from the cancer registry. Descriptive statistics were used to analyze the interval cancers and the \( \chi^2 \) test statistic was used to analyze differences in the distribution of cancer stage and cancer location between screen-detected cancers of the first and the second round and interval cancers. Data were analyzed using the statistical software SPSS 18.0 (SPSS Inc, Chicago, IL).

Results

Invitation and Participation

Figure 1 shows the flow of participants through the program. Between June 2006 and February 2007, 5015 persons were randomly allocated to a first-round invitation with the guaiac FOBT and 5039 to an invitation with the FIT. Of those invited, 2119 allocated to the guaiac FOBT and 5039 to an invitation with the FIT. Of those invited, 2119 allocated to the guaiac FOBT and 5039 to an invitation with the FIT (57%) (\( P < .0002 \)). The mean age of participants in the first round was 60 years; 43% were male (Table 1).

Of these 4990 first-round participants, 755 persons (15%) were excluded from an invitation to the second round based on either a first-round positive test result (293) or noneligibility (497), leaving 4200 persons eligible for the second round. Of these, 3616 invitees (86%) also participated in the second round; 1594 (44%) had performed a guaiac FOBT in the first round and 2022 (56%) a FIT. The mean age of second-round participants was 61 years; 43% were male (Table 1).

Positivity Rate

Positivity rates in the first and second round are shown in Table 2. The positivity rate in the group of persons that had performed a FIT in both the first and the second round did not differ significantly between rounds: 8.1% in the first round versus 7.4% in the second round (\( P = .34 \)). No significant difference in second-round positivity was observed with regard to the type of test used in the first round: 7.4% in the FIT-after-FIT group and 8.5% in the FIT-after-guaiac FOBT group (\( P = .22 \)).

FIT positivity rates within the first and second round were higher for male than for female subjects, but these differences were not statistically significant (\( P = .74 \) and \( P = .36 \), respectively).

Colonoscopy Procedures

Of all participants who tested positive and were eligible for colonoscopy, 239 of 293 (82%) with a first-round positive result and 252 of 284 (89%) with a second-round positive result underwent the procedure. Of those not followed up by colonoscopy, the majority of persons (54%) did not undergo the procedure because of (medical) contraindications, most often severe comorbidity, or because they recently had a bowel examination. Only a minority of those with an FIT-positive result did not show up for the information consultation or chose not to undergo a colonoscopy after attending the information consultation (10% and 36%, respectively).

Cecal intubation was achieved in 227 procedures (95%) in the first round and in 234 procedures (93%) in the second round (these are crude intubation rates unadjusted for poor bowel preparation, colonic stricture, equipment failure, or severe endoscopic colitis). Mean withdrawal time, including polypectomy, was 17 minutes (±13) and 23 minutes (±18), respectively. The most frequent reasons for an incomplete procedure were residual stool and patient discomfort. Six complications were observed: five cases of delayed bleeding and one perforated diverticulum in a person with diverticulitis at colonoscopy.

Colonoscopy Findings

Table 3 shows the most advanced lesion at colonoscopy per participant. In both rounds, advanced adenomas were the most common finding: 47% in the first round and 41% in the second round. The distribution of the type of lesions detected by colonoscopy in first-round participants was similar for the guaiac FOBT and for the FIT (\( P = .35 \)). The corresponding distribution in the second round did not significantly differ between the FIT-after-FIT group and the FIT-after-guaiac FOBT group (\( P = .81 \)).

Advanced Adenomas

Table 4 shows the total number of persons with an advanced adenoma as the most advanced lesion, specified by advanced features. Most of the advanced adenomas were
classified as such based on size. Mean overall adenoma size did not differ between the first round and the second round: 14 ± 2 mm in the first round versus 14 ± 10 mm in the second round (P = .85). Most lesions were located distally, including 75% of those detected in the first round and 66% in the second round. As can be appreciated from Table 4, relatively more adenomas were found proximally with FIT than with guaiac FOBT (27% vs 17%).

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>First round</th>
<th></th>
<th>Second round</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>Mean ± SD (y)</td>
<td>No. of male subjects (%)</td>
<td>No. of</td>
</tr>
<tr>
<td></td>
<td>participants</td>
<td></td>
<td></td>
<td>participants</td>
</tr>
<tr>
<td>Guaiac FOBT</td>
<td>2119</td>
<td>60 ± 7</td>
<td>896 (42)</td>
<td>FIT</td>
</tr>
<tr>
<td>FIT</td>
<td>2871</td>
<td>60 ± 7</td>
<td>1299 (45)</td>
<td>FIT</td>
</tr>
<tr>
<td>Total</td>
<td>4990</td>
<td>60 ± 7</td>
<td>2195 (43)</td>
<td>Total</td>
</tr>
</tbody>
</table>

Figure 1. Flowchart.
Cancers

Table 5 displays the characteristics of the cancers detected in the screening pilot. In the first screening round, 20 cancers were screen detected: 8 after a positive guaiac FOBT result and 12 after a positive FIT result. In the second round, 9 cancers were screen detected: 5 after a negative guaiac FOBT result in the first round and 4 after a negative FIT result.

A total of 10 interval cancers were diagnosed between screening rounds. Eight were observed after a previous negative test result in the first round: 4 after a negative guaiac FOBT and 4 after a negative FIT. One cancer was most likely missed at colonoscopy; one other cancer was diagnosed in a person who had not undergone a colonoscopy after a positive FIT result because of attribution of the blood loss by the general practitioner to known hemorrhoids. The median interval between screening and diagnosis was 18 months (range, 3–23 months).

The stage distribution of the cancers was similar for screen-detected and interval cancers ($P = .63$). The distribution of the location of the cancers in the colon was also similar ($P = .30$); the majority of cancers was located distally (60%–73%).

PPV

Table 6 shows the estimated PPVs for CRC and for advanced neoplasia. The PPV for advanced neoplasia was lower in the second round: 44% versus 55% ($P = .017$). The second-round PPV for advanced neoplasia was 48% in the FIT-after-guaiac FOBT group and 42% in the FIT-after-FIT group.

The PPV for CRC was 4% in the second round versus 8% in the first round ($P = .024$). Results were comparable between second-round subgroups: 4% in the FIT-after-guaiac FOBT group and 3% in the FIT-after-FIT group.

For comparison, Table 6 also shows the PPVs at hypothetical cutoff levels of 75 or 100 ngHb/mL. As expected, the PPV of FIT for advanced neoplasia increases with higher cutoff levels. The increase in PPV would be accompanied by a lower detection rate. In FIT users only, using a cutoff level of 100 ngHb/mL would have missed 27 advanced adenomas and one cancer in the first round and 20 advanced adenomas and no cancers in the second round. At this cutoff level, 84% and 85% of advanced adenomas detected at a cutoff level of 50 ngHb/mL (Table 4).

We also looked at the distribution of lesion location: 77% and 70% of advanced adenomas detected at 100 ngHb/mL were located distally versus 73% and 62% of adenomas detected at a cutoff level of 50 ngHb/mL. The one cancer that would have been missed at a cutoff level of 100 ngHb/mL in the first round was a stage I cancer located in the ascending colon.

The FIT PPV for advanced neoplasia was higher in male than in female subjects in both screening rounds: 61% versus 46% in the first round (relative PPV, 0.75; 95% confidence interval, 0.57–0.99) and 50% versus 33% in the second round (relative PPV, 0.66; 95% confidence interval, 0.43 to 1.00). The FIT PPV for CRC was similar in male and female subjects.

Discussion

In the first 2 rounds of a Dutch CRC screening pilot, using a FIT or guaiac FOBT in the first round and...
FIT in the second round, we did not observe a significant decrease in FIT positivity rate in the second round. In the second round, however, fewer cases of advanced neoplasia were detected after a positive test result, and the chances of finding CRC were halved: from 8% in the first round to 4% in the second round.

A limitation of our study is that we do not have conclusive data on the reasons why persons accepted or declined the invitation to participate in our screening program and whether or not symptoms were among these reasons. A second potential limitation is the quality of the bowel preparation, which could be scored as excellent or good in only 77% and 61% of procedures in the first and second round, respectively. This could have resulted in advanced neoplasms missed at colonoscopy and an underestimation of FIT performance characteristics. Despite the large numbers, our sample size does not allow for a precise estimation of smaller changes in positivity and predictive values in the subgroups of FIT-after-guaiac FOBT and FIT-after-FIT users. We should also add that this study could not evaluate FOBT sensitivity, because we did not perform colonoscopies in those with a negative screening. It is possible that the PPV is high given the presumably low sensitivity.

In this study we observed a much larger decrease in PPV for CRC than for advanced neoplasia, the vast majority of which consisted of advanced adenomas cases. These findings imply that the FOBT is better at detecting cancers than at identifying advanced adenomas, a finding in line with results from several other studies that previously reported a higher sensitivity of FOBT for CRC than for advanced adenomas. The difference in the detection of advanced adenomas and cancers seems to be much more pronounced in guaiac FOBTs than in immunochemical tests. Several other studies also concluded that the FIT performed better than expectations in the detection of advanced adenomas. As a result, the sensitivity of the FIT for advanced adenomas is a little less than one-third of its sensitivity for CRC. As a result, a substantial number of advanced adenomas are detected in second-round participants after having received a negative test result in the first round. However, in a screening program, missing cancers is more worrisome than missing advanced adenomas. Most likely, adenomas progress slowly to can-

### Table 4. Advanced Adenomas

<table>
<thead>
<tr>
<th>Advanced features</th>
<th>Guaiac FOBT (n = 24)</th>
<th>FIT (n = 88)</th>
<th>Overall (n = 112)</th>
<th>FIT after guaiac FOBT (n = 53)</th>
<th>FIT after FIT (n = 50)</th>
<th>Overall (n = 103)</th>
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</thead>
<tbody>
<tr>
<td>&gt;10 mm</td>
<td>21 (87)</td>
<td>66 (75)</td>
<td>87 (78)</td>
<td>39 (74)</td>
<td>38 (76)</td>
<td>77 (75)</td>
</tr>
<tr>
<td>6–9 mm with high-grade dysplasia or villous component</td>
<td>2 (8)</td>
<td>12 (14)</td>
<td>14 (13)</td>
<td>4 (8)</td>
<td>4 (8)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>0–5 mm with high-grade dysplasia or villous component</td>
<td>1 (4)</td>
<td>10 (12)</td>
<td>11 (10)</td>
<td>10 (19)</td>
<td>8 (16)</td>
<td>18 (17)</td>
</tr>
</tbody>
</table>

**Location**

<table>
<thead>
<tr>
<th>Location</th>
<th>First round (n = 112)</th>
<th>Second round (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Guaiac FOBT (n = 24)</td>
<td>FIT after guaiac FOBT (n = 53)</td>
</tr>
<tr>
<td>Proximal</td>
<td>3 (45)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Distal</td>
<td>6 (40)</td>
<td>3 (30)</td>
</tr>
</tbody>
</table>

**NOTE.** All values are expressed as n (%).

### Table 5. Cancers

<table>
<thead>
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<th>Stage at diagnosis</th>
<th>First round</th>
<th>Interval cancers</th>
<th>Second round</th>
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<tr>
<td></td>
<td>Guaiac FOBT (n = 8)</td>
<td>FIT after negative guaiac FOBT (n = 4)</td>
<td>Overall (n = 20)</td>
</tr>
<tr>
<td>I</td>
<td>3 (45)</td>
<td>1 (25)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>II</td>
<td>2 (20)</td>
<td>1 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>III</td>
<td>2 (30)</td>
<td>0 (0)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>3 (30)</td>
</tr>
</tbody>
</table>

**Location**

<table>
<thead>
<tr>
<th>Location</th>
<th>First round</th>
<th>Interval cancers</th>
<th>Second round</th>
</tr>
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<tr>
<td></td>
<td>Guaiac FOBT (n = 8)</td>
<td>FIT after negative guaiac FOBT (n = 4)</td>
<td>Overall (n = 20)</td>
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<tr>
<td>Proximal</td>
<td>2 (40)</td>
<td>2 (50)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Distal</td>
<td>6 (60)</td>
<td>5 (50)</td>
<td>12 (60)</td>
</tr>
</tbody>
</table>

**NOTE.** All values are expressed as n (%).

Cancers diagnosed in first-round participants outside the screening program but within the screening interval.

Cecum, ascending colon, hepatic flexure, transverse colon, or splenic flexure.

Descending colon, sigmoid colon, or rectum.
cer; annual progression rates of 0.25% and 1% have been reported.24–26

The actual prevalence of advanced neoplasia in screening populations is largely unknown. Regula et al reported 5.9% of cases in persons aged 50 to 66 years.27 If so, it could be argued that the vast majority of advanced adenomas and cancers detected in our second screening round were lesions missed in the first round. Because of the previously described superior sensitivity for advanced neoplasia of FIT over the guaiac FOBT, we were somewhat surprised to detect a similar proportion of advanced neoplasia cases in the second round after a negative guaiac FOBT result or after a negative FIT result in the first round. Apparently, the short duration of the pilot and the limited sensitivity of occult blood tests for advanced adenomas did not result in a measurable difference.

We do not know if the significant decrease in PPV over 2 screening rounds will continue in future screening rounds. In a Scottish screening study using guaiac FOBT, both the PPV for advanced neoplasia and the PPV for CRC did not decrease further after the second round; however, in the Danish study, the PPV for advanced neoplasia continued to decrease gradually up to the fifth screening round.3,28 The latter supports our hypothesis that a longer period is necessary to show a more prominent decrease in prevalence, because program sensitivity increases with consecutive screening rounds.

Furthermore, we chose a relatively low cutoff level for FIT positivity compared with other studies and it is very well possible that in further screening rounds positivity rates will stay relatively high, resulting in many colonoscopy procedures, whereas PPV will decrease further. By choosing a higher cutoff level, burden on capacity will be less. The choice for a cutoff level will be a fine balance between these 2 parameters and will be influenced by economic, behavioral, and other parameters and differ per country.

In these first 2 screening rounds, no significant decrease in mean size of advanced adenoma or cancer stage at diagnosis was observed; however, the number of screen-detected cancers was fairly small, making definitive conclusions difficult.

A total of 10 interval cancers were diagnosed. The issue of interval cancers and missed adenomas and cancers could raise the question about a subset of advanced neoplasias that are more likely to be missed than others. A study by Morikawa et al showed that the sensitivity of FIT is higher for distal cancers than for proximal cancers.7 Guittet et al showed that bleeding amounts for high-risk adenomas of the proximal colon were similar to those for small adenomas or normal colonic mucosa.18 In our study, the majority of advanced adenomas and cancers were located distally. This was not different in the group of interval cancers, which were also predominantly located distally (70%).

In conclusion, the results reported here show that, despite a significant decrease in the PPV for CRC in a second round of screening, a substantial number of significant lesions are detected in a second screening round. This applies more to advanced adenomas than to cancer cases and appears to be independent of the type of test used in the first round (guaiac FOBT or FIT). The fact that we observed no differences in PPV between participants who had performed a guaiac FOBT in the first round and those who had performed a FIT in the first round indicates that differences between the 2 tests should not be overestimated and that no large difficulties are to be expected should a switch from a guaiac FOBT-based program to a FIT-based program be desired in screening programs currently using guaiac FOBTs.

References